(3*S*)-3-[(3*S*)-2-Oxo-3-(3-phenylpropionylamino)-5-(3-phenylpropionyl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609a).

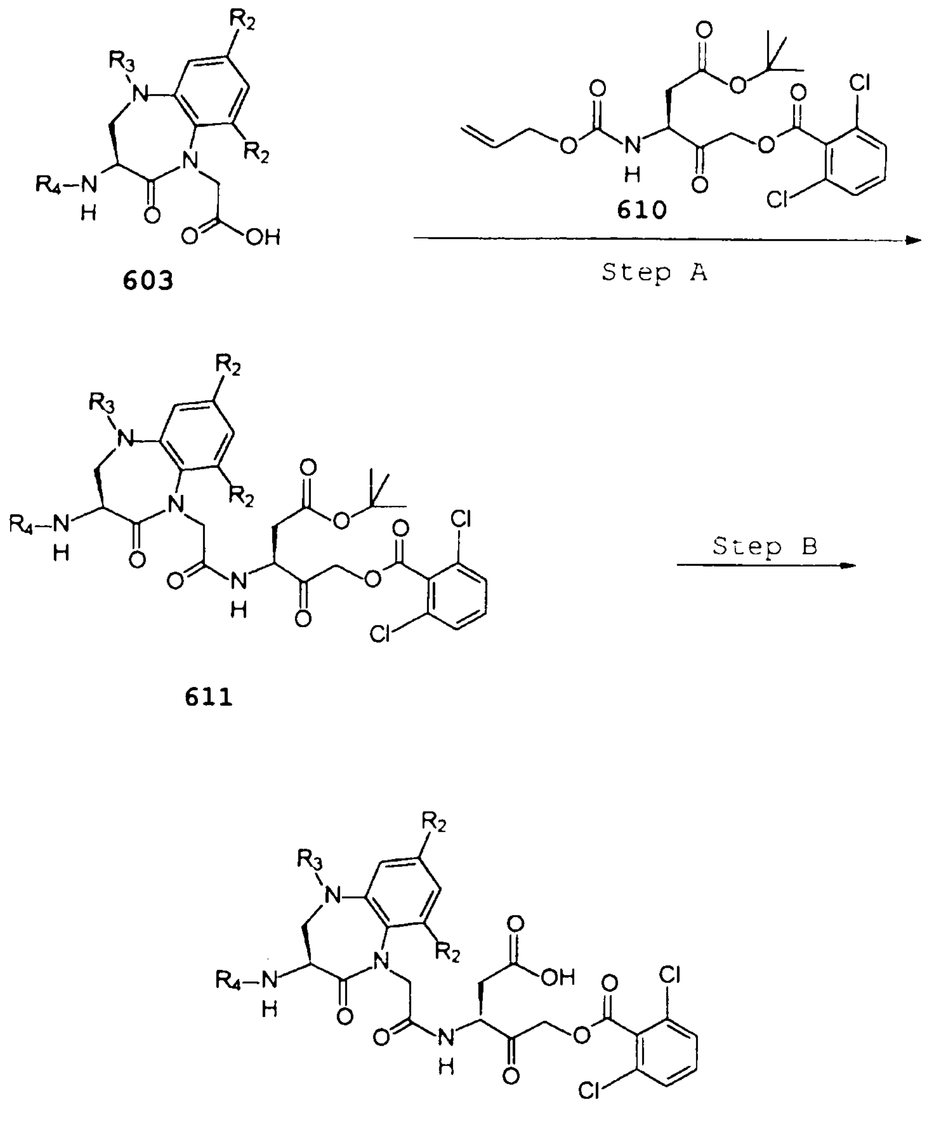
Step A. A solution of **204** (223 mg, 0.5 mmol) and **603r** (300mg; 0.36 mmol) in 4 ml of DMF and 4 ml of CH_2Cl_2 was treated with $(Ph_3P)_2PdCl_2$ (10 mg), 1-hydroxybenzotriazle (135 mg, 1.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (115 mg, 0.6 mmol). Tri-n-butyl tin hydride (219 mg, 0.75 mmol) was added dropwise to the reaction and stirred for 18 h. The reaction was poured onto EtOAc and washed with aq. 10% $NaHSO_4$, sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (flash, SiO_2, 0% to 50% EtOAc/hexane) gave 360 mg (86%) of **607a** as a foam.

Step B. A solution of **607a** (360 mg) in 5 ml of CH_2Cl_2 was added dropwise to a suspension of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodioxol-3(1H)-one (362 mg, 0.85 mmol) in 20 ml of CH_2Cl_2. The reaction was stirred for 4.5 h, diluted with CH_2Cl_2 and washed with a 1:1 mixture of sat. aq. $NaHCO_3$/sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$ (2x) and sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (flash, SiO_2, 20% EtOAc/CH_2Cl_2) gave 340 mg (95%) of the ketone **608a**.

Step C. **608a** (300 mg, 0.36 mmol) was dissolved in 25 ml of 25% TFA/CH_2Cl_2 and stirred at RT for 5 h and concentrated *in vacuo*. Chromatography (flash, SiO_2, 0 to 5% MeOH/CH_2Cl_2) gave 118 mg (42%) of **609a** as a white solid: ^1H NMR (CD_3OD) δ 7.62-6.65 (16H, m), 4.85-4.7

(1H, m), 4.68-4.42 (2H, m), 4.40-4.15 (2H, m), 3.48-3.28 (1H, m), 3.0-2.9 (1H, m), 2.9-2.6 (4H, m), 2.55-2.18 (3H, m), 2.16-1.96 (2H, m).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-acetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-1-acetylamino]-4-(5,7-dichlorobenzoxazol-2-yl)-4-oxo-butyric acid (609b) was prepared from **603d** in a similar manner as **609a** to give 287 mg (43% overall yield) as white solid: ^{1}H NMR(DMSO-d_6) δ 1.6(s, 3H), 2.7-3.1(m, 2H), 3.45(m, 1H), 4.4(t, 1H), 4.7(m, 2H), 4.95(m, 1H), 5.2, 5.4(2s, 1H), 7.2-7.65(m, 8H), 7.9(d, 2H), 8.8(t, 1H), 8.9,9.1(2s, 1H), 12.6(br, 1H).



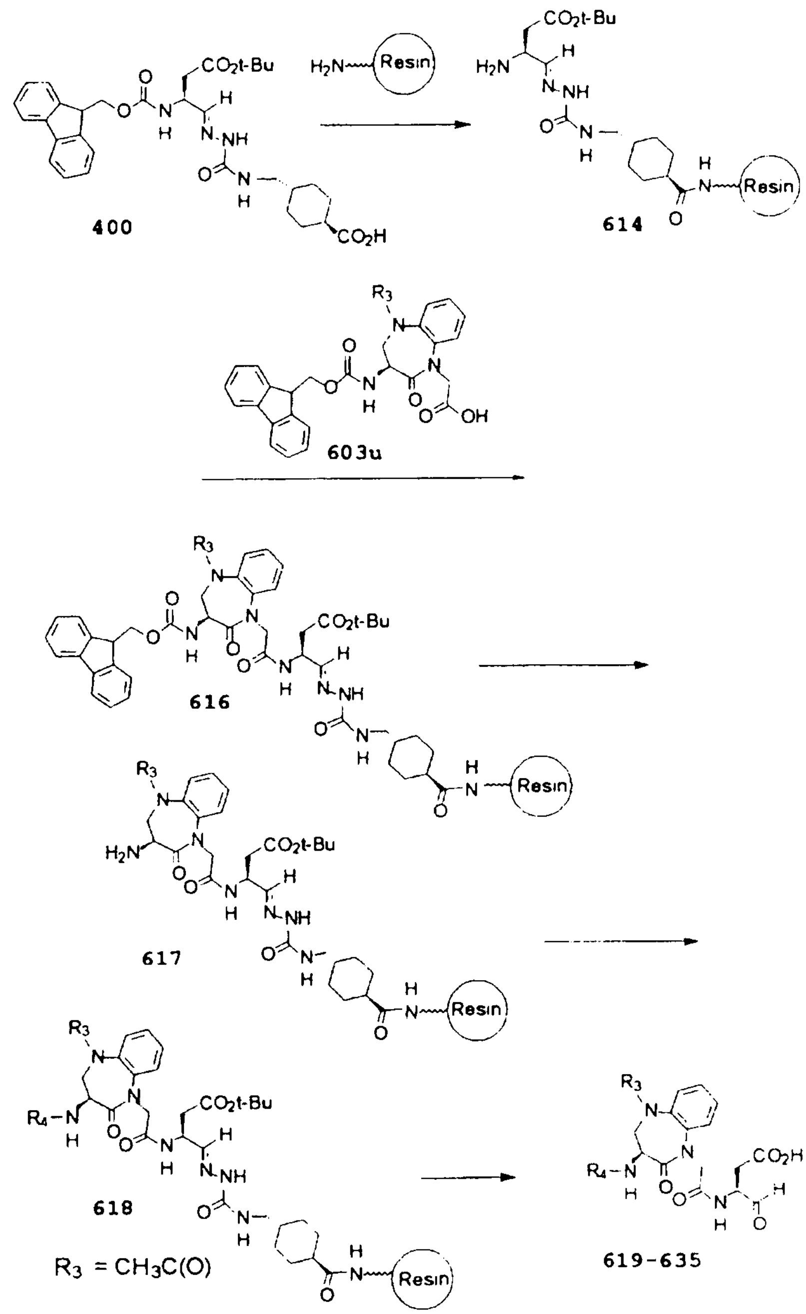
612

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-methanesulfonyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine-1-acetylamino]-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (**612**) was prepared by a method similar as **607a** (Steps A and C only) using **603m** (150 mg, 0.36 mmol)

instead of **603r** and (3*S*)-3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoic acid *t*-butyl ester (110; 160 mg, 0.36 mmol, WO 93/16710) instead of **606a** to give **612** (56%) as a white solid: ^{1}H NMR ($CDCl_3$) 7.85-7.10 (12H, m), 5.4-4.65 (4H, m), 4.6-4.15 (4H, m), 3.10-2.72 (5H, s & m).

Example 13

Compounds **619-635** were synthesized as described in Example 13 and Table 14.


400
614
603u
616
617
618
619-635
CO2t-Bu
H2N
Resin
R3
R4
R3 = CH3C(O)

Syntheses of 619-635.

Step A. Synthesis of 614. TentaGel S® NH_2 resin (0.16 mmol/g, 10.0 g) was placed in a sintered glass funnel and washed with dimethylformamide (3 X 50 mL), 10% (v/v) diisopropylethylamine (DIEA) in dimethylformamide (2 X 50 mL) and finally with dimethylformamide (4 X 50 mL). Sufficient dimethylformamide was added to the resin to obtain a slurry followed by **400** (1.42 g, 2.4 mmol, prepared from (3S) 3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)), 1-hydroxybenzotriazole hydrate ($HOBT{\cdot}H_2O$; 0.367 g, 2.4 mmol), O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 0.91 g, 2.4 mmol), and DIEA (0.55 mL, 3.2 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin was isolated on a sintered glass funnel by suction filtration and washed with dimethylformamide (3 X 50 mL). Unreacted amine groups were then capped by reacting the resin with 20% (v/v) acetic anhydride/dimethylformamide (2 X 25 mL) directly in the funnel (10 min/wash). The resin was washed with dimethylformamide (3 X 50 mL) and dichloromethane (3 X 50 mL) prior to drying overnight *in vacuo* to yield **614** (11.0 g, quantitative yield).

Step B. Synthesis of 616. Resin **614** (3.0 g, 0.16 mmol/g, 0.48 mmol) was swelled in a sintered glass funnel by washing with dimethylformamide (3 X 15 mL). The Fmoc protecting group was then cleaved with 25% (v/v) piperidine/dimethylformamide (15 mL) for 10 min

(intermittent stirring) and then for 20 min with fresh piperidine reagent (15 ml). The resin was then washed with dimethylformamide (3 X 15 ml), followed by N-methypyrrolidone (2 X 15 mL). After transferring the resin to a 100 mL flask, N-methypyrrolidone was added to obtain a slurry followed by **603u** (0.736 g, 0.72 mmol), HOBT·H_2O (0.112 g, 0.73 mmol), HBTU (0.27 g, 0.73 mmol) and DIEA (0.26 mL, 1.5 mmol). The reaction mixture was agitated overnight at room temperature using a wrist arm shaker. The resin work-up and capping with 20% (v/v) acetic anhydride in dimethylformamide were performed as described for **614** to yield **616** (3.13 g, quantitative yield).

Step C. Synthesis of 617. This compound was prepared from resin **616** (0.24 g, 0.038 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (3 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **617**. The resin was washed with dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL).

Step D. Method 1. (624). Resin **617** was acylated with a solution of 0.4M thiophene-3-carboxylic acid and 0.4M HOBT in N-methypyrrolidone (1 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.35 mL) and the reaction was shaken for 2 hr at room temperature. The acylation step was repeated. Finally, the resin was washed with dimethylformamide (3 X 1 mL), dichloromethane (3 X 1 mL) and dried *in vacuo*.

The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H2O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 ether:pentane (12 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H2O/0.1% TFA (15 mL) and lyophilized to obtain crude **624** as a white powder. The compound was purified by semi-prep RP-HPLC with a Rainin Microsorb™ C18 column (5 u, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 45 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **624** (10.0 mg, 54%).

Step D. Method 1A. Synthesis of 627. Following a similar procedure as method 1, resin **617** was acylated with 4-(1-fluorenylmethoxycarbonylamino)benzoic acid and repeated. The Fmoc group was removed as described in Step C and the free amine was acetylated with 20% (v/v) acetic anhydride in dimethylformamide (1 mL) and 1.6M DIEA in N-methylpyrrolidone (0.35 mL) for 2 hr at room temperature. The acetylation step was repeated. Cleavage of the aldehyde from the resin gave **627** (4.2 mg, 20%).

Step D. Method 2. Synthesis of 632. Following a similar procedure as method 1, resin **617** was acylated with 0.5M cinnamoyl chloride in N-methypyrrolidone (1 mL) and 1.6M DIEA in N-methypyrrolidone (0.35 mL) for 2 hr at room temperature. The acylation step was

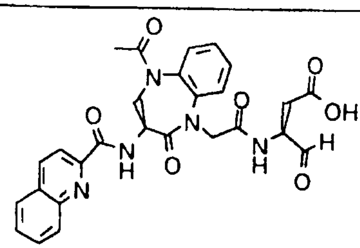
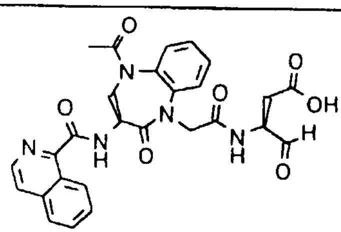
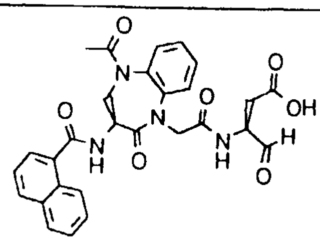
repeated. Cleavage of the aldehyde from the resin gave **632** (11.1 mg, 58%).

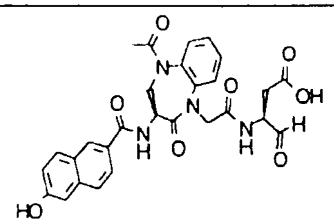
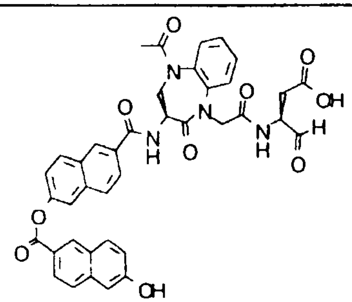
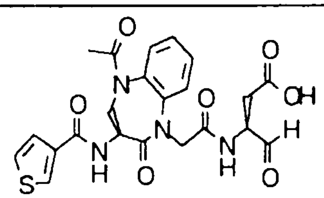
Step D. Method 3. Synthesis of 629. Following a similar procedure as method 1, resin **617** was reacted with 1.0M benzenesulfonyl chloride in dichloromethane (0.5 mL) and 1M pyridine in dichloromethane (0.60 mL) for 4 hr at room temperature. The reaction was repeated. Cleavage of the aldehyde from the resin **629** (4.7 mg, 24%).

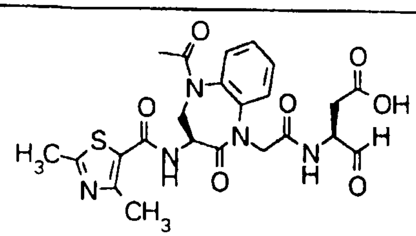
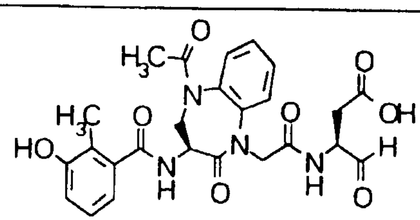
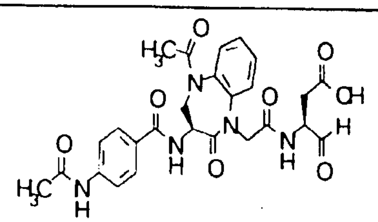
Analytical HPLC methods:

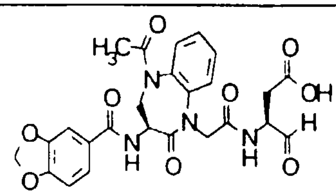
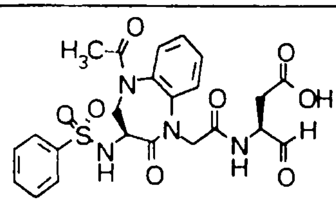
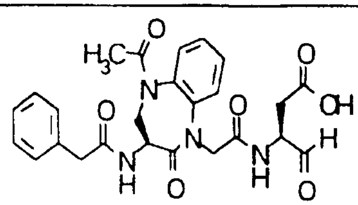
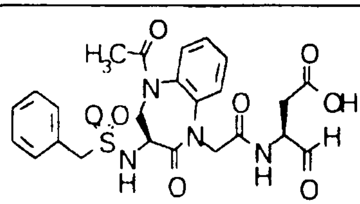
(1) Waters DeltaPak C18, 300A (5u, 3.9 X 150 mm). Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

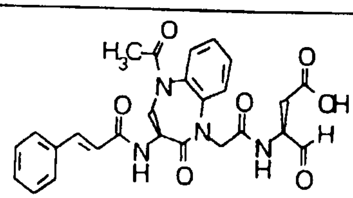
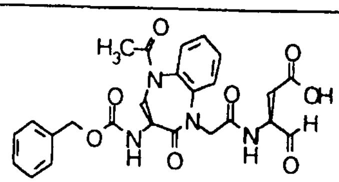
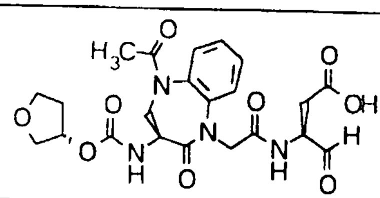
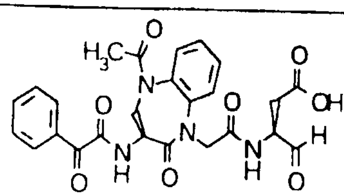
Table 14

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
619		C27H25N5O7	531.53	11.71 (1) 98%	532	1
620		C27H25N5O7	531.53	10.44 (1) 98%	532	1
621		C28H26N4O7	530.54	11.57 (1) 98%	(M+Na)+ 553	2

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
622		C28H26N4O8	546.54	10.19 (1) 98%	(M+Na)+ 569	1
623		C39H32N4O10	716.71	15.8 (1) 09%	(M-) 716	1
624		C22H22N4O7S	486.51	8.39 (1) 98%	487	1

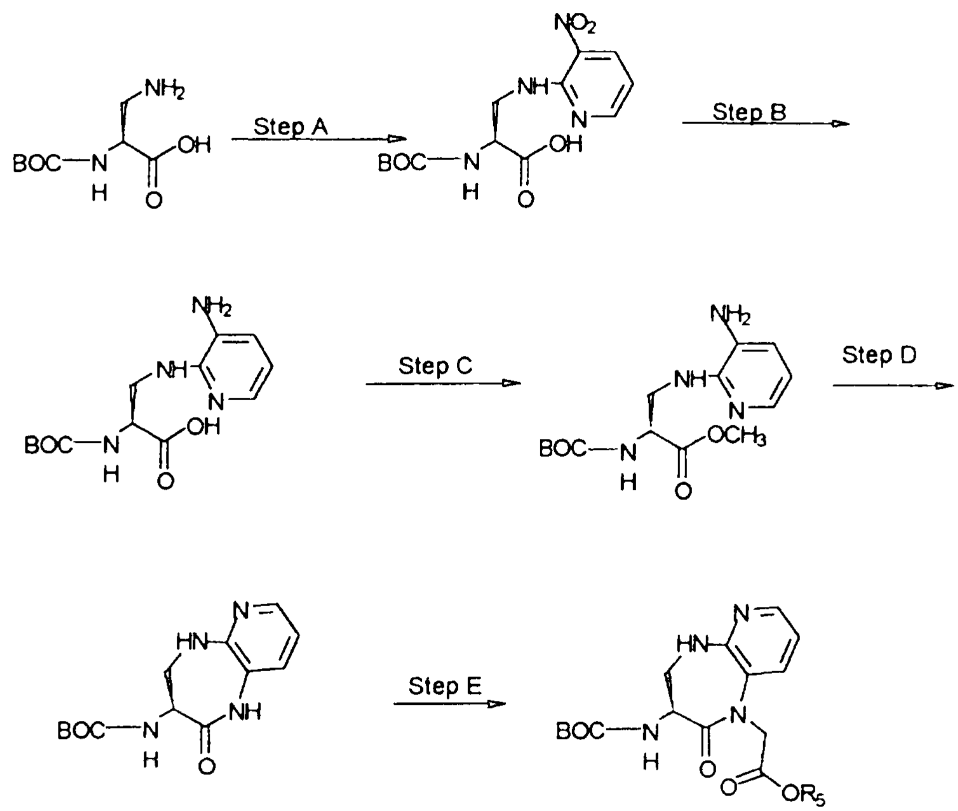
Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
625		C23H25N5O7S	515.55	7.60 (1) 98%	516	1
626		C25H26N4O8	510.51	7.58 (1) 98%	511	1
627		C26H27N5O8	537.53	7.96 (1) 98%	538	1A

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
628		C25H24N4O9	524.49	9.50 (1) 98%	525	1
629		C23H24N4O8S	516.53	9.85 (1) 98%	517	3
630		C25H26N4O7	494.51	9.25 (1) 98%	495	2
631		C24H26N4O8S	530.56	10.19 (1) 98%	531	3

Cmpd.	Structure	MF	MW	HPLC RT min	MS (M+H)+	Syn. Method
632		C26H26N4O7	506.52	10.99 (1) 98%	507	2
633		C25H26N4O8	510.51	11.48 (1) 98%	511	2
634		C22H26N4O9	490.47	6.87 (1) 98%	491	2
635		C25H24N4O8	508.49	10.03 (1) 98%	509	1

Example 14

Compounds **1605a-j**, **1605m**, **1605n**, **1605p**, **1605t**, and **1605v** were synthesized as described below.



(3*S*) N-(2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1H-pyrido [3,4-b][1,4-diazepine (1600).

Step A. (2*S*) 2-*tert*-Butoxycarbonylamino-3-(3-nitropyridin-2-ylamino)propionic acid was prepared by a similar method as (2S) 2-*tert*-butoxycarbonylamino-3-(2-nitrophenyl-amino)propionic acid in Step A of the synthesis of **600a/103**, except that 3-chloro-3-nitro pyridine was used instead of 2-

fluoronitrobenzene, to give 4.05 g (64%) of a yellow solid.

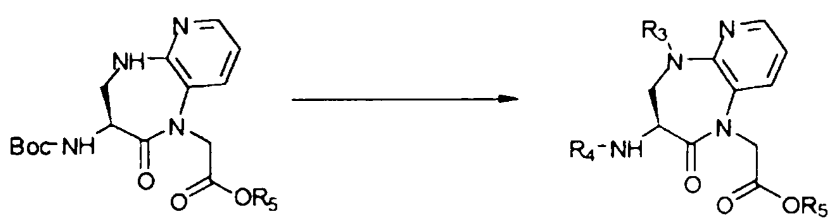
Step B. (2*S*) 2-*tert*-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid was prepared by a similar method to (2*S*) 2-*tert*-Butoxycarbonylamino-3-(2-aminophenylamino)-propionic acid in Step B of the synthesis of **600a/103** to give 3.68 g (quant.) as a dark solid.

Step C. (2S) 2-*tert*-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid methyl ester. A solution of (2S) 2-*tert*-Butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)-propionic acid (360 mg, 1.21 mmol) and MeOH (59 mg, 1.82 mmol) in anhydrous CH_2Cl_2 (20 ml) was treated with 4-dimethylaminopyridine (DMAP, 163 mg, 1.33 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (280 mg, 1.45 mmol). The reaction was stirred for 18 h, diluted with EtOAc (150ml), washed with water (2x), sat. aq. $NaHCO_3$, and sat. aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (flash, SiO_2, 0 to 5% $MeOH/CH_2Cl_2$) gave 250 mg (67%) of the title compound as a light tan solid.

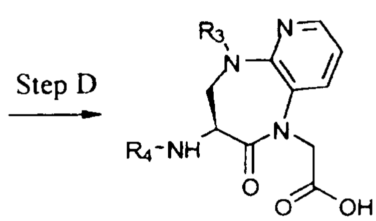
Step D. (3S) N-(2-Oxo-3-*tert*-butoxycarbonylamino-2,3,4,5-tetrahydro-1H- pyrido[3,4-b][1,4-diazepine (1600). A solution of (2S) 2-*tert*-butoxycarbonylamino-3-(3-aminopyridin-2-ylamino)propionic acid methyl ester (70 mg, 0.225 mol) and 25% sodium methoxide/MeOH (130 µl, 0.56 mmol) in anhydrous MeOH (4 ml) was heated at 60°C for 16 h.

The reaction was concentrated *in vacuo*, the residue dissolved in 2 ml of H_2O and extracted with EtOAc (3x). The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (flash, SiO_2, 0 to 3% MeOH/CH_2Cl_2) gave 7.5 mg (3%) of **1600** as a light tan solid: ^1H NMR (CD_3OD) δ 7.96-7.92 (1H, d), 7.75-7.65 (1H, br. s), 7.14-7.08 (1H, d), 6.73-6.65 (1H, m), 5.83-5.75 (1H, br. s), 5.4-5.25 (1H, br. s), 4.6-4.5 (1H,m), 3.95-3.84 (1H, m), 3.55-3.48 (1H, m), 1.4 (9H, s)

Step E. **1601** is prepared from **1600** following the method in Step D for the preparation **600a/103**.

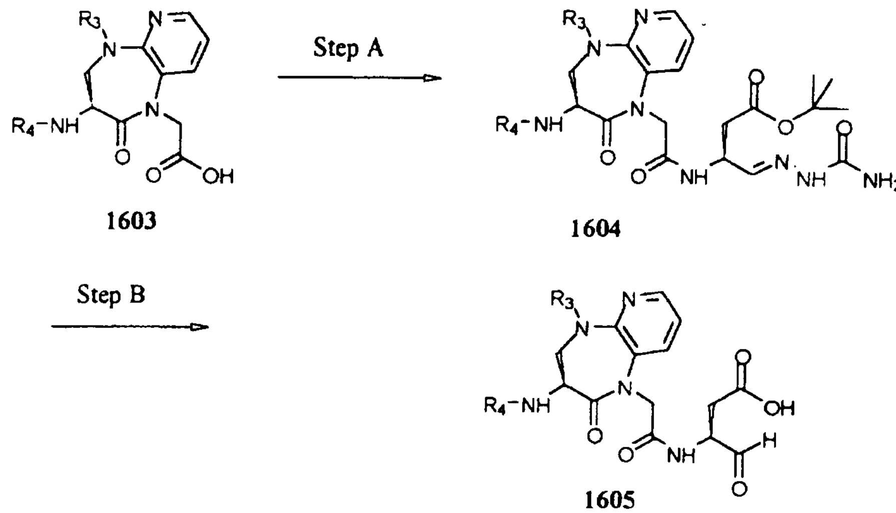


1601 **1602**



1603

Synthesis of 1603. **1603** is prepared from **1601** following the methods for the synthesis of **603** from **600**.



Synthesis of 1605. **1605** is prepared from **1603** by methods described for the synthesis of **605** from **603**.

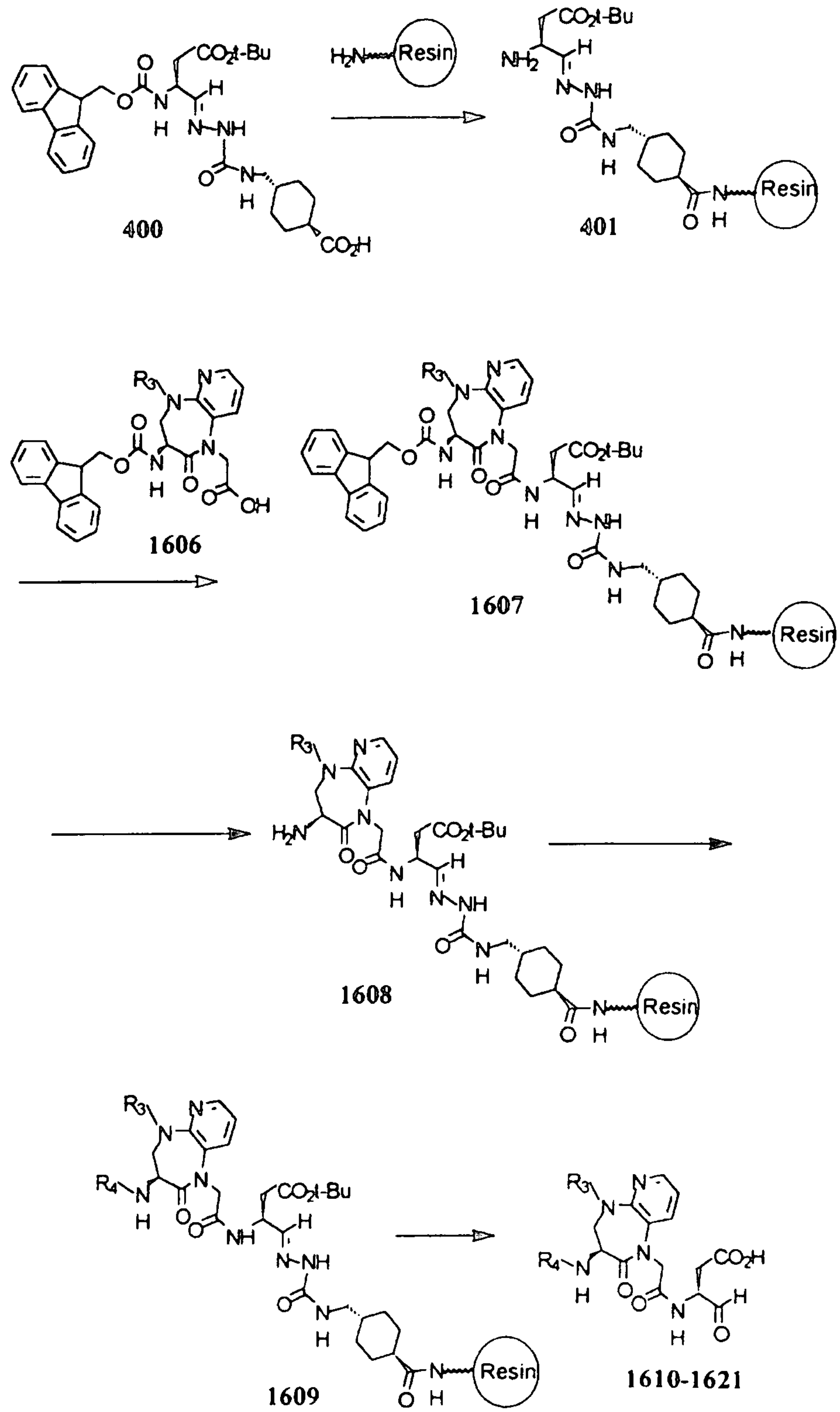
Table 15

1605	R_3	R_4
a	$PhCH_2CH_2CO$	PhCO
b	$PhCH_2CO$	PhCO
c	PhCO	PhCO
d	CH_3CO	PhCO
e	CH_3OCH_2CO	PhCO
f	$(CH_3)_2CHCH_2CO$	PhCO
g	CH_3COCH_2CO	PhCO
h	CH_3OCOCO	PhCO
i	CH_3COCO	PhCO
j	CH_3OCO	PhCO
m	CH_3SO_3	PhCO
n	CH_3CO	Naphthyl-2-CO
p	$PhCH_2NHCO$	PhCO

t	3-CH_3PhCH_2CO	PhCO
v	$PhCH_2CH_2CO$	$PhCH_2$

Example 15

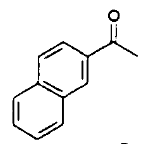
Compounds **1610-1621** are prepared from **1600** by methods similar to the methods used to prepare compounds **619-635** from **600a/103** and **600b**.

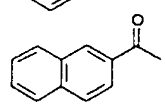

400
401
1606
1607
1608
1609
1610-1621

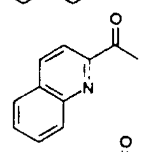
wherein for compounds **1610-1621**,

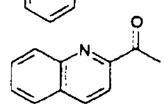
a R_3 = $CH_3C(O)$-
b R_3 = $CH_3OCH_2C(O)$-:

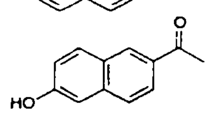
$\underline{R_4}$

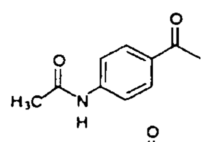
1610 

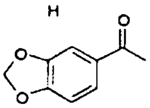
1611 

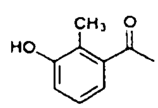
1612 

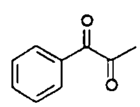
1613 

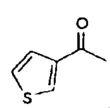
1614 

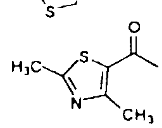
1615 

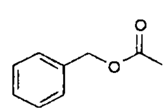
1616 

1617 

1618 

1619 

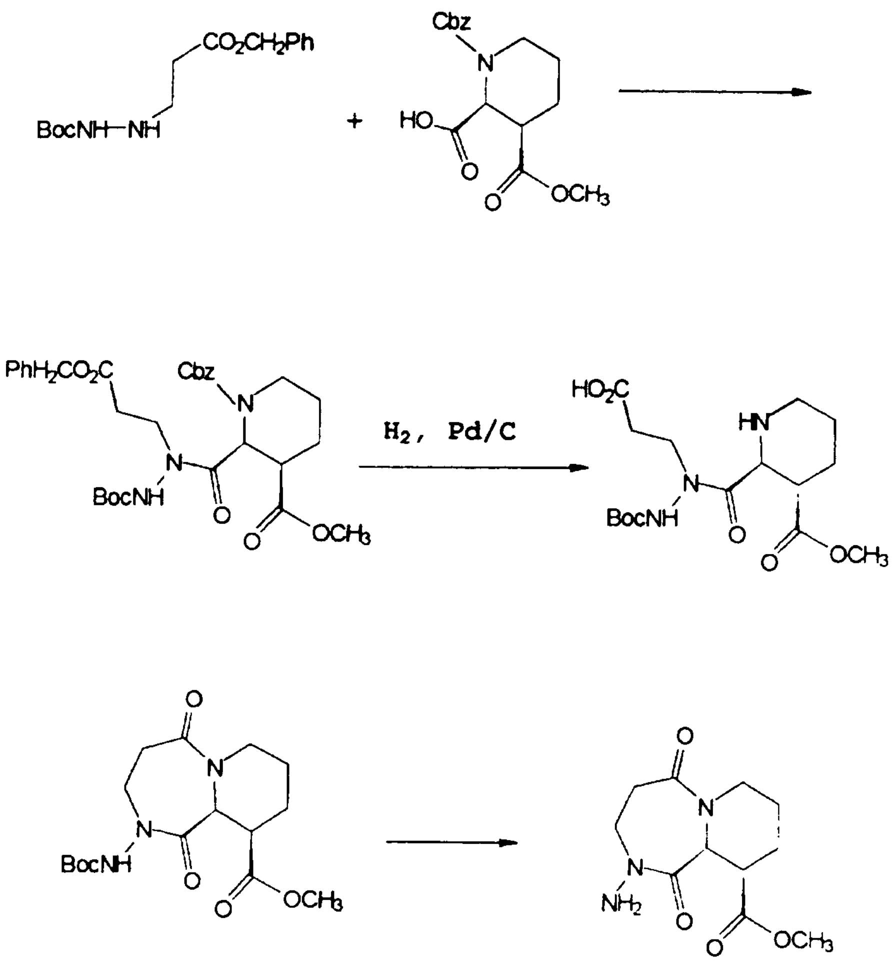
1620 

1621 

Example 16

Compounds comprising scaffolds (e11), (y1), (y2), (z), and (e12) may be synthesized as described below.

Synthesis of Scaffold R_1, wherein R_1 is (e11) and wherein Y_2 is =O.



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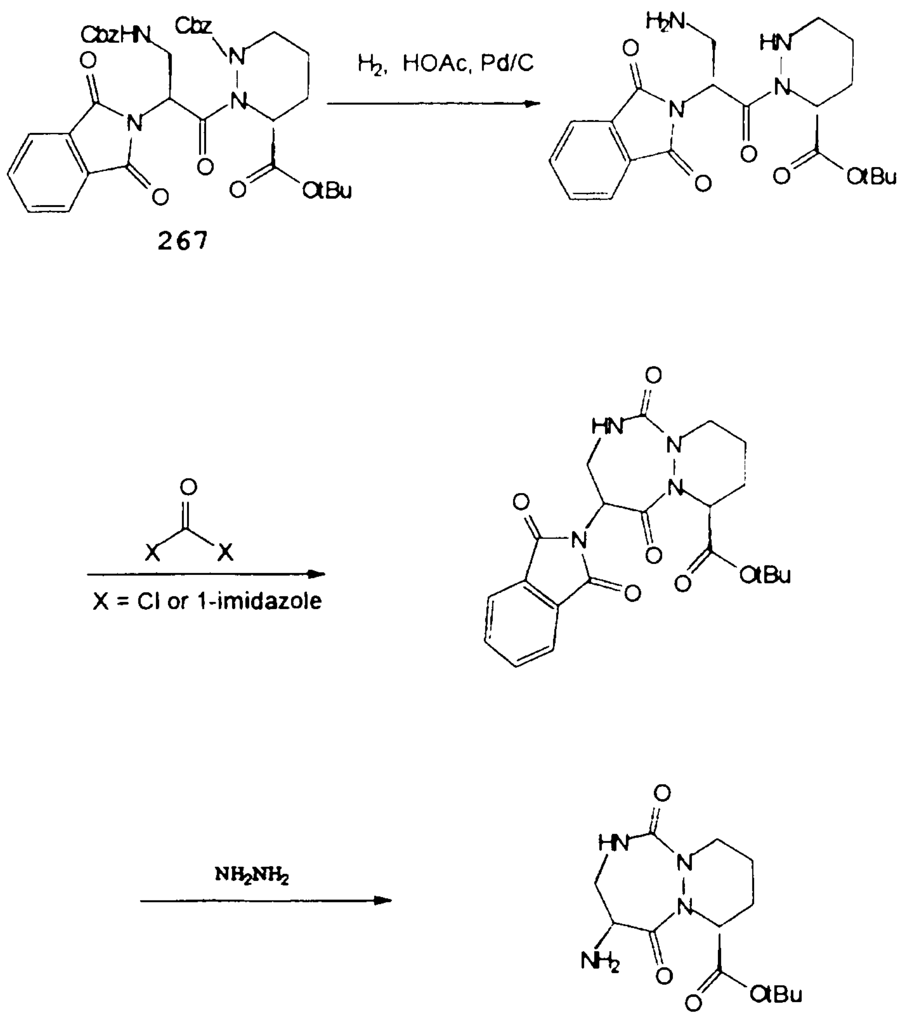
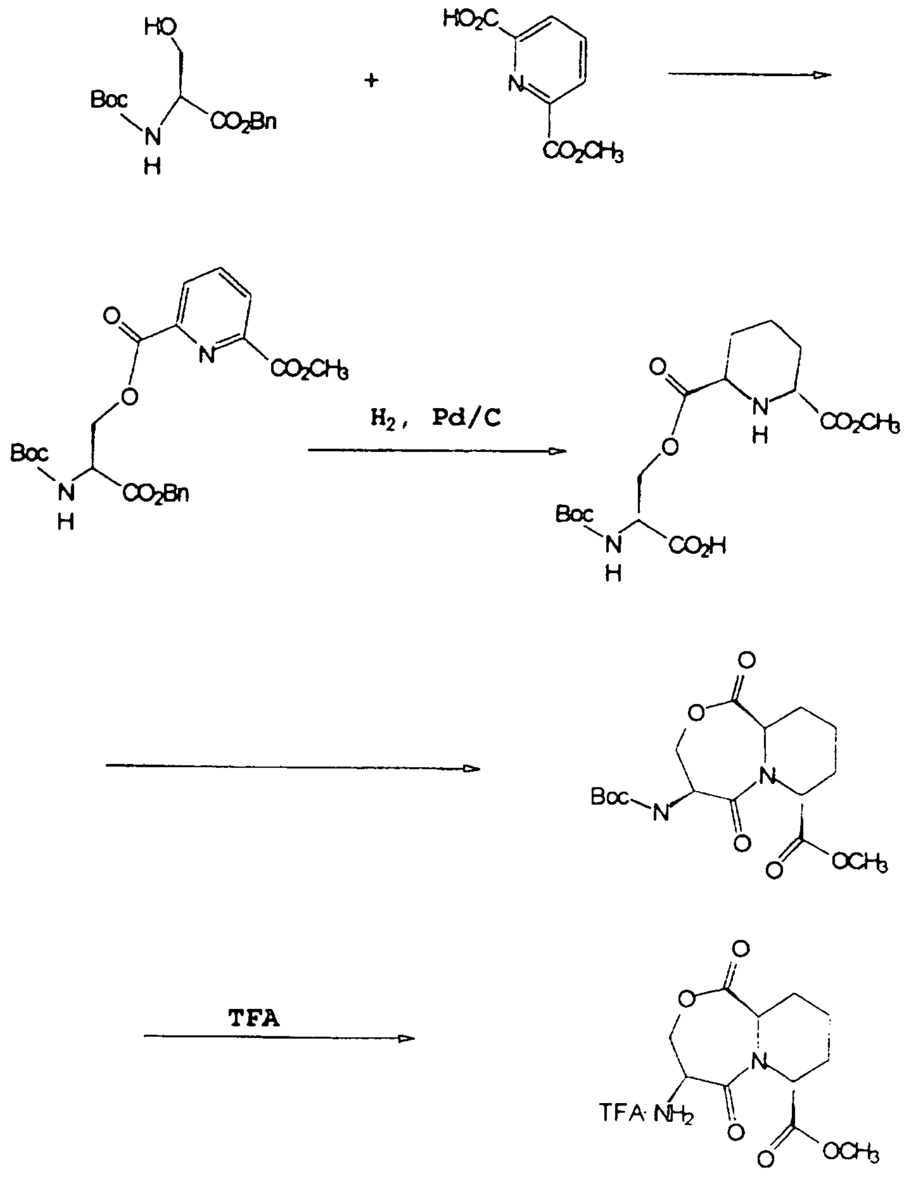
Synthesis of Scaffold R_1, wherein R_1 is (y1) and wherein Y_2 is =O.



267

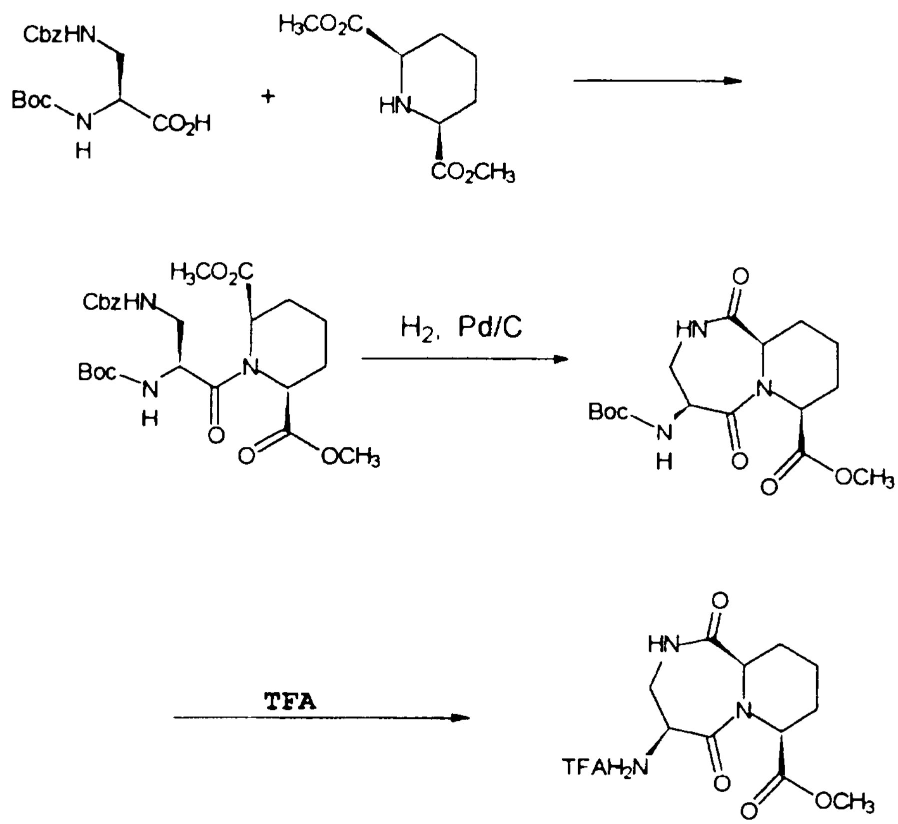
270

Synthesis of Scaffold R_1, wherein R_1 is (y2) and wherein Y_2 is H_2 and X_7 is O.



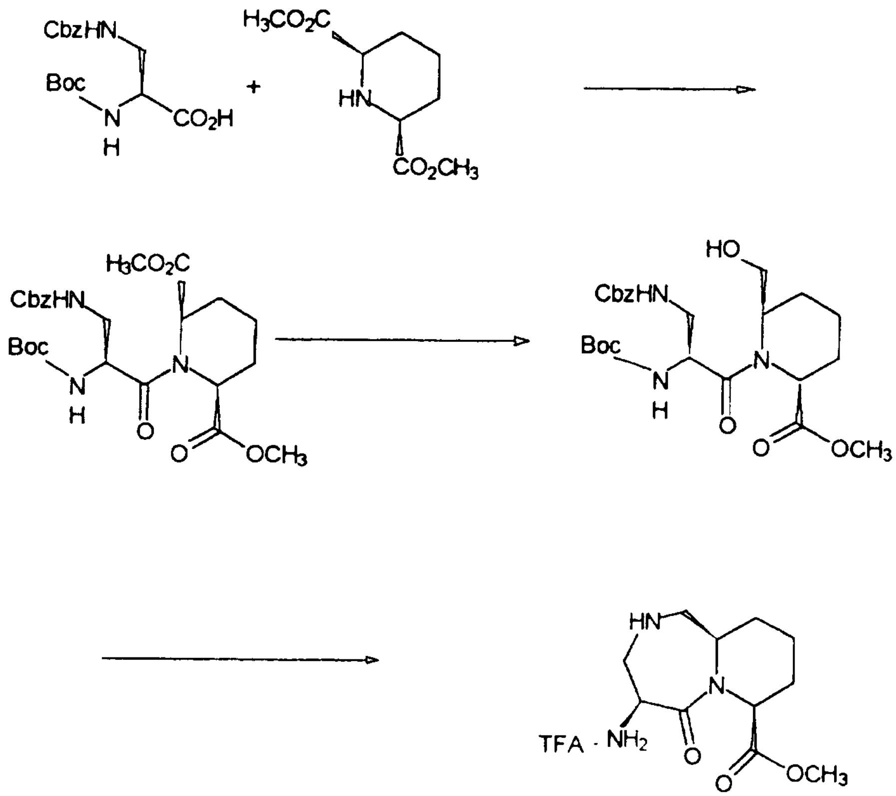
273

Synthesis of Scaffold R_1, wherein R_1 is (y2) and wherein Y_2 is =O and X_7 is NH.



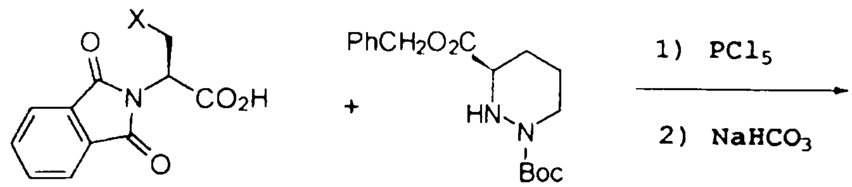
271

Synthesis of Scaffold R_1, wherein R_1 is (y2) and wherein Y_2 is H_2 and X_7 is NH.

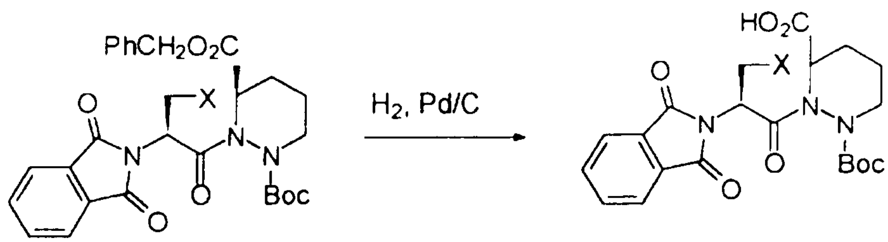


272

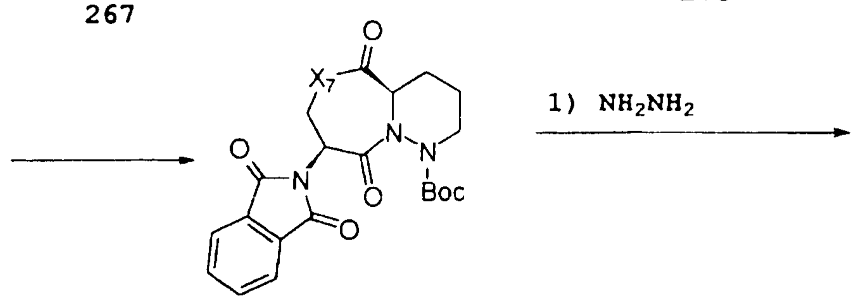
Synthesis of Scaffold R_1, wherein R_1 is (z) and wherein Y_2 is O.

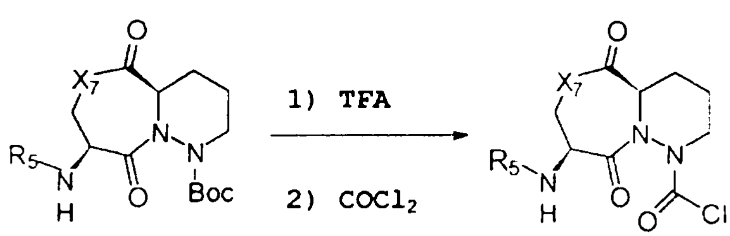


X = NHCbz
X = OCH_2Ph



267 270

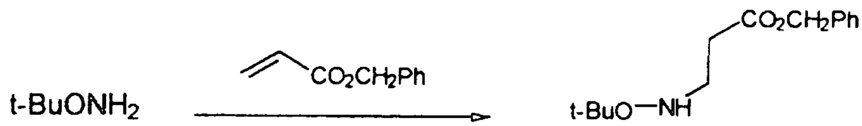




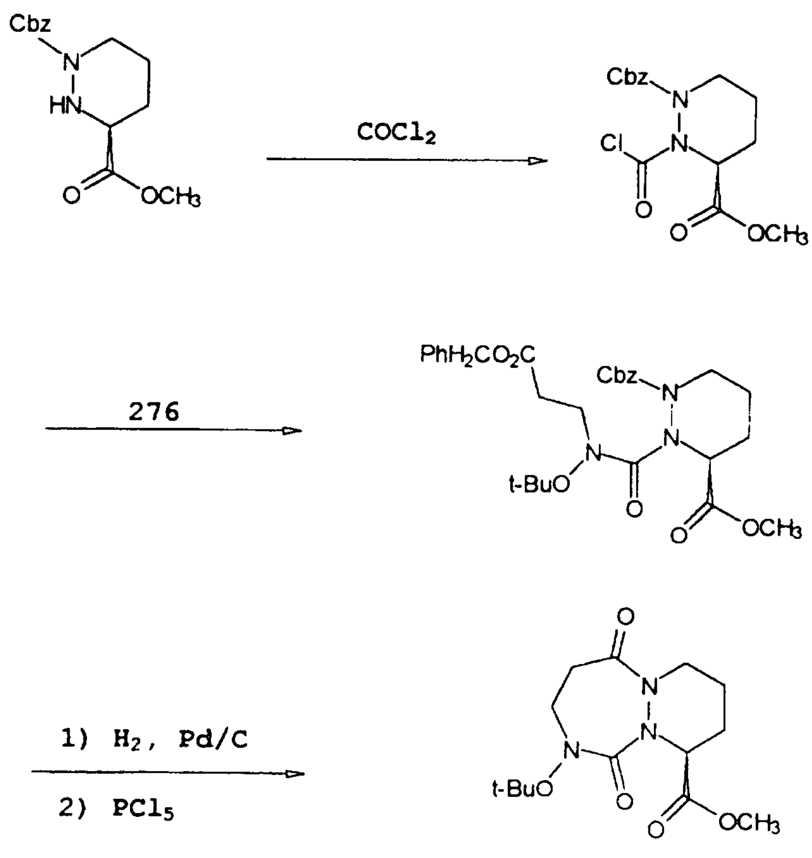
271

274 X_7 = NH
275 X_7 = O

Synthesis of Scaffold R_1, wherein R_1 is (e12) and wherein Y_2 is =O.



276



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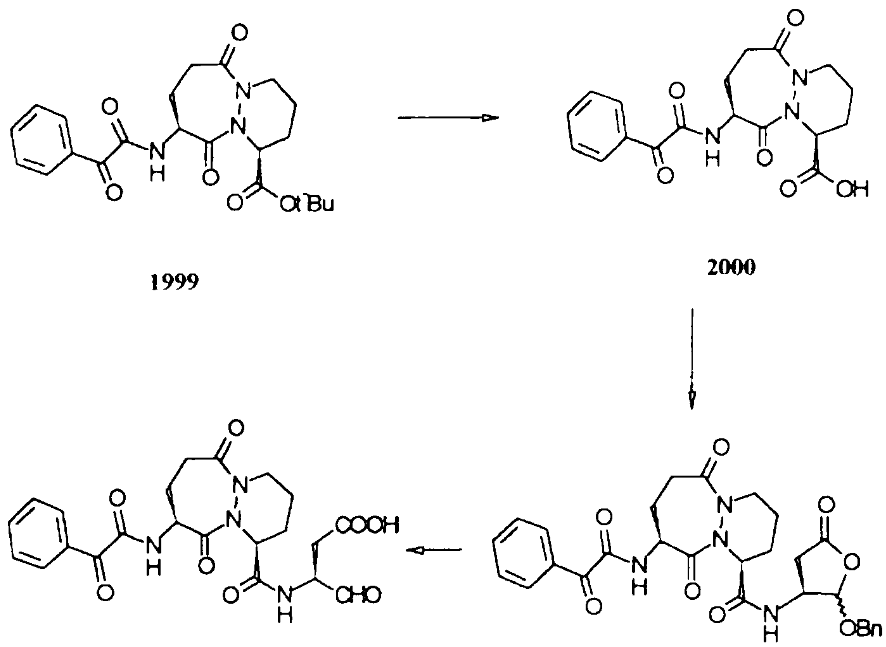
Example 17

The preparation of compounds **2001**, **2002**, **2100a-e**, and **2201** is described below.



1999 **2000** **2002** **2001**

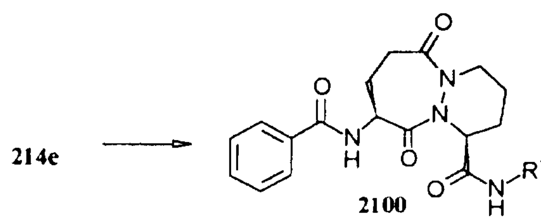
(1*S*,9*S*) 9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a]-[1,2] diazepine-1-carboxylic acid (2000). To a solution of t-butyl 9-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (GB 2,128,984; 340 mg, 1.15 mmol) in CH_2Cl_2 was added benzoylformic acid (260 mg, 1.7 mmol), HOBT (230 mg, 1.7 mmol) and EDC (340 mg, 1.7 mmol). The resulting mixture was stirred at ambient temperature for 16 hours, poured into 1N HCl and extracted with CH_2Cl_2. The organic extracts were

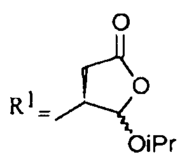
further washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to afford **1999** as a pale yellow solid. The solid was dissolved in CH_2Cl_2 (25 ml) and TFA (25 ml) and stirred overnight and concentrated in vacuo to give 560 mg of **2000** as an oil.

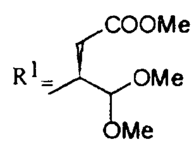
[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2(*R,S*)-benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamide (2001), was synthesized from **2000** by methods similar to compound **213e** to afford 410 mg (63%) of **2001** as a white solid: ^1H NMR ($CDCl_3$; mixture of diastereomers) δ 8.25 (1H, d), 8.23 (1H, d), 7.78 (1H, dd), 7.65 (1H, bm), 7.50 (2H, m), 7.40-7.25 (4H, m), 6.55 (1H, d), 5.57 (1H, d), 5.10 (1H, t), 5.05-4.95 (2H, m), 4.90, (1H, d), 4.80 (1H, d), 4.72 (1H, bm), 4.65 (1H, m), 4.55 (1H, m), 4.45 (1H, t), 3.25 (1H, m), 3.15 (1H, m), 3.00 (2H, bm), 2,90 (1H, dd), 2.70 (1H, m), 2.47 (1H, dd), 2.45 (1H, m), 2.35 (1H, m), 2.00-1.75 (4H, m), 1.60 (1H, bm).

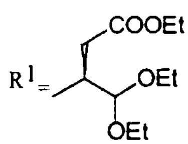
[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4-oxobutanoic acid (2002). Compound **2001** (58.6 mg, 0.10 mmol) was treated with 15 ml of TFA/MeCN/water (1:2:3) and stirred at room temperature for 6.5 h. The reaction was extracted with ether. The aqueous layer was concentrated with azeotropic removal of the water using MeCN. The product was suspended in CH_2Cl_2, concentrated in vacuo and precipitated with ether to give 46.8 mg

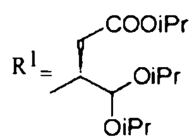
(99%) of **2002** as a white solid: ^{1}H NMR (CD_3OD) δ 9.05 (0.25H, d), 8.15 (1H, d), 7.68 (1H, t), 7.64 (0.25H, d), 7.55 (3H, t), 7.35 (0.5H, m), 5.22 (1H, t), 4.90 (1H, m), 4.58 (1H, dd), 4.50 (1H, m), 4.28 (1H, bm), 3.45 (1H, m), 3.10 (1H, bt), 2.68 (1H, ddd), 2.60-2.45 (2H, m), 2.30 (1H, dd), 2.15-2.05 (2H, m), 1.90 (2H, bm), 1.68 (1H, bm).



2100a 

2100c 

2100b 

2100d 

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-isopropoxy-5-oxo-tetrahydro-furan-3-yl)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxamide (2100a). A solution of **214e** (101 mg, 0.23 mmol) in isopropanol (10 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (10 mg). After 75 minutes, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and

concentrated. Flash chromatography (SiO_2, CH_2Cl_2 to EtOAc) afforded 56 mg (51%) of **2100a** as a white solid: ^1H NMR ($CDCl_3$; mixture of diastereomers) δ 7.9-7.8 (2H,m), 7.6-7.5 (1H, m), 7.5-7.4 (2H, m), 7.1 (0.5H, d), 6.9 (0.5H, d), 6.4 (0.5H,d), 5.6 (0.5H, d), 5.3 (0,5H, s), 5.2-5.1 (1H, m), 4.95 (0.5H, m), 4.75-4.5 (1.5H, m), 4.35 (0.5H, t), 4.1 (0.5H, m), 3.98 (0.5H, m), 3.3-2.75 (4H, m), 2.5-2.4 (2H,m), 2.25 (1H, m), 2.1-1.9 (3H,m) 1.75-1.55 (2H,m).

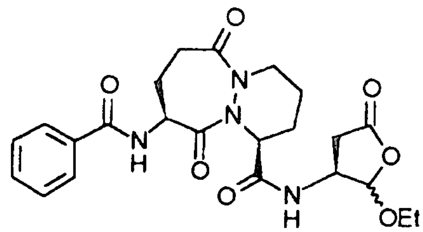
[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-diethoxy-butyric acid, ethyl ester (2100b). A solution of **214e** (16 mg, 0.036 mmol) in ethanol (2 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (2 mg). After 5 days, the reaction mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2, CH_2Cl_2:EtOAc 95:5 v/v) afforded 16 mg (81%) of **2100b** as a white solid: ^1H NMR ($CDCl_3$) d 7.85-7.74 (2H,m), 7.55-7.38 (3H,m), 7.04-6.95 (1H,d), 6.61-6.48 (1H,d), 5.15-5.08 (1H,m), 4.63-4.53 (1H,m), 4.52-4.45 (1H,m), 4.42-4.35 (1H,m), 4.15-4.05 (2H,m), 3.74-3.60 (2H,m), 3.57-3.42 (2H,m), 3.39-3.28 (1H,m), 3.03-2.93 (1H,m), 2.92-2.82 (1H,m), 2.65-2.52 (2H,m), 2.42-2.25 (1H,m), 2.20-1.88 (4H,m), 1.76-1.50 (2H,m), 1.35-1.10 (9H,m).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-dimethoxy-butyric acid

methyl ester (2100c). A solution of **214e** (165 mg, 0.37 mmol) in methanol (5 ml) was stirred at room temperature with a catalytic amount of *p*-toluenesulfonic acid (17.5 mg). After 4 days, the reaction mixture was diluted with EtOAc and washed with 10% $NaHCO_3$ (3x) and brine. The combined extracts were dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2, EtOAc) afforded 127 mg (68%) of **2100c** as a white solid: ^1H NMR ($CDCl_3$) δ 7.82 (2H, d), 7.55-7.50 (1H, m), 7.47-7.43 (2H, m), 7.02 (1H, d), 6.53 (1H, d), 5.20-5.10 (1H, m), 4.56-4.50 (1H, m), 4.45-4.50 (1H each, two m), 3.69 (3H, s), 3.41 (3H, s), 3.43 (3H, s), 3.35-3.25 (1H, m), 3.06-2.98 (1H, m), 2.94-2.83 (1H, m), 2.65-2.53 (2H, m), 2.35-2.32 (1H, m), 2.15-2.07 (1H,m), 2.00-1.89 (3H, m), 1.75-1.56 (2H, m).

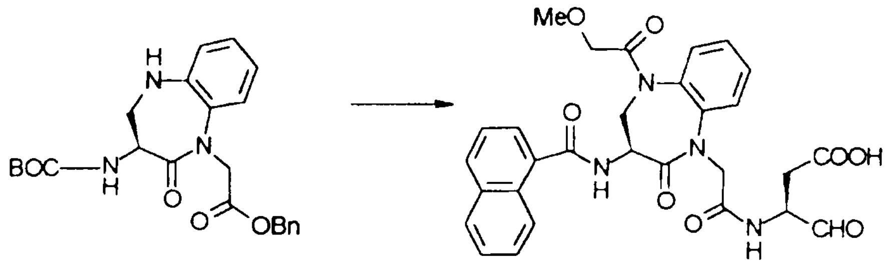
[3*S*(1*S*,9*S*)] 3-(9-Benzoylformylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamido)-4,4-diisopropoxy-butyric acid, isopropyl ester (2100d). A solution of **214e** (53 mg, 0.12 mmol) in isopropanol (5 ml) was stirred at 50 °C with a catalytic amount of *p*-toluenesulfonic acid (5 mg). After 3 days the reaction mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated. Flash chromatography (SiO_2, CH_2Cl_2:EtOAc (4:1 to 1:1 v/v)) afforded 49 mg (68%) of **2100d** as a white solid: ^1H NMR ($CDCl_3$) δ 7.85 (2H, d), 7.50-7.43 (1H, m), 7.41-7.35 (2H, m), 7.02 (1H, d), 6.47 (1H, d), 5.13-5.07 (1H, m) 5.00-4.9 (1H, m), 4.61-4.55 (2H, m), 4.37-4.30(1H, m), 3.80-3.70 (1H, m), 3.90-3.80 (1H, m), 3.42-3.35 (1H, m),

3.03-2.93 (1H, m), 2.91-2.81 (1H, m), 2.62-2.50 (2H, m), 2.38-2.33 (1H, m), 2.12-2.06 (1H,m), 1.97-1.81 (3H, m), 1.70-1.60 (2H, m), 1.28-1.05 (18H,m).



2100e

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxo-tetrahydro-furan-3-yl)-6H-pyridazino[1,2-a][1,2]-diazepine-1-carboxamide (2100e), was synthesized from **302** via methods used to synthesize **304a** to afford **2100e**, except ethanol and triethylorthoformate were used instead of methanol and trimethylorthoformate. Chromatography (SiO_2, 5% ethanol/CH_2Cl_2) afforded 92 mg (68%) of a white solid: ^1H NMR ($CDCl_3$; mixture of diastereomers) δ 7.90-7.80 (2H, m), 7.60-7.50 (1H, m), 7.50-7.40 (2H, m), 7.30 (0.5H, d), 7.00 (0.5H, d), 6.50 (0.5H, d), 5.50 (0.5H, d), 5.20-5.10 (1.5H, m), 4.95 (0.5H, m), 4.75-4.65 (0.5H, m), 4.65-4.50 (1H, m), 4.38 (0.05H, t), 4.00-3.90 (0.5H, m), 3.85-3.75 (0.5H, m), 3.75-3.65 (0.5H, m), 3.65-3.55 (0.5H, m), 3.30-2.70 (4H, m), 2.50-2.35 (2H, m), 2.30 (1H, d), 2.15-1.90 (3H, m), 1.80-1.60 (2H, m), 1.25-1.20 (3H, two t)



600b

2201

(3*S*)-3-[(3*S*)-2-oxo-3-(1-naphthoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (2201) was synthesized from **600b** by the methods used to synthesize **605b** to afford **2201**: ^{1}H NMR ($CDCl_3$) δ 8.30-8.22 (1H,m), 8.05-7.98 (1H, d), 7.96-7.83 (1H,m), 7.77-7.68 (1H,m), 7.67-7.40 (7H,m), 5.12-5.02 (1H,m), 4.98-4.41 (5H,m), 4.38-4.24 (1H,m), 4.07-4.00 (1H,d), 3.92-3.80 (2H,m), 3.32 (3H,s), 2.75-2.60 (1H,m), 2.58-2.35 (1H,m).

Example 18

We obtained the following data for selected compounds of this invention using the methods described herein (Table 16, see Example 7; Tables 17 and 18, see Examples 1-4). The structures and preparations of compounds of this invention are described in Examples 28-31.

Table 16 Comparison of Prodrugs for Efficacy in LPS Challenged Mice: Inhibition of IL-1β Production. The percent inhibition of IL-1β production after treatment with a compound of the invention is shown as a function of time after LPS challenge ("-" indicates that no value was obtained at that relative time).

Time of Compound Administration (relative to time of LPS challenge, PO, 50 mg/kg)

Compound	-2h	-1h	0h	+1h
213f	(-4)	-	8	-
213h	9	-	53	-
213i	(-11)	-	62	-
213k	0	-	68	-
213l	(-18)	-	80	-
213m	26	-	42	-
213o	4	-	8	-
213p	21	-	29	-
213q	17	-	91	-
213r	59	-	37	-
213x	0	-	78	-
213y	29	-	50	-
214e	39	-	70	75
	43	44	48	11
	-	-	-	47
214k	12	-	31	-
214l	0	-	54	-
214m	0	-	17	-
214w	11	-	91	-
264l	0	-	23	-
404	-	-	-	56
	55	-	6	-

Compound	-2h	-1h	0h	+1h
412	0	-	0	-
	11	-	37	-
418	-	-	-	64
	25	-	52	-
434	-	-	-	80
	0	-	63	-
450	0	-	35	-
452	-	-	-	70
	28	-	89	-
456	-	-	-	56
	41	-	69	-
470	0	-	36	-
471	0	-	34	-
475	0	-	15	-
481	27	-	0	-
486	19	-	15	-
487	17	-	20	-
528	25	-	67	-
550f	0	-	50	-
550h	55	-	73	-
550i	(-10)	-	23	-
550k	36	-	34	-
550l	9	-	38	-
550m	45	-	52	-
550n	19	-	65	-
550o	19	-	64	-
550p	30	-	60	-
655	0	-	68	-
656	31	-	16	-
662	41	-	75	-
668	-	-	-	53
695a	49	-	78	-
1015	15	-	28	-
2001	64	62	58	55
2001a	10	-	16	-
2002	5	-	87	-
2100h	34	-	32	-
2100i	19	-	74	-
2100j	48	41	0	33
2100k	30	50	32	72
2100l	52	-	28	-
2100m	40	-	42	-
2100n	21	9	64	73
2100o	31	44	68	64

Table 17 Data for selected compounds of this invention obtained using the methods described in Examples 1-4.

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
213f			3000		
213g			2200		
213h			1500		
213i			1100		
213j					
213k			2000		
213l			2000		
213m			2500		
213o		5000	3300		
213p			<300		
213q			<300		
213r			<300		
213v	0.5	1,100	1100	41	23
213x		4500	2500		
213y			930		
214j	4.2	2500	6000		
214k	0.2	500	580		22
214l	6	1900	1100		12
214m	1.5	530	2200		33.4
214w	0.6	620	370		15
246b	30000	>30000		87	
264l			3000		
265a	2600	25000			
265c	1100	4500			32
265d	500	1500			35
265f	1200				24
280b		13000			
280c		10000			86
280d		25000			
283b		1750			41
283c		4000			50

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50(nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
283d		>8000	10000		
308c	3000				
308d	3000				
500	25	1800	1800		
501	2.5	1800	1600		
505c		1500			
505d		>20000			
505f		550			
510a	65	200		267	
510d	2300	>20000			
511c	730	>20000		78	40
528			2200		
550f			1100		
550h			1800		
550i			1400		
550k			3000		
550l			750		
550m			2000		
550n			<300		
550o		450	3000		
550p			2900		
550q			700		
640	155	2250	3900		
642	35	8000	2900		
645	150				
650	550	4000			
653	30	2300	6000		
655					
656	0.6	2100	1600		2.9
662	0.5	1800	800		2.75
668	9	5200	3700		29
669	14		10000		
670			4500		
671	5	2000	2500		33.2
677			610		
678	5	2700	2200		
680					

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
681	9	3000	5000		
682			1300		
683	400	>20000	>20000		
684	15	5000	2800		
686	4	4000	9000		
688a			3000		
688b			1300		
689a	0.8	910	2500		
689b	2.2	600	2000		
690a			1600		
690b					
691a	2.1	2900	1200		9.9
691b	11.5	1,900	1400		
692a					
692b			1800		
693					
694	3	2600	2100		
695a					
695b					
695c			2500		
696	4.5	2000	2900		13
700	275				
701	90				
702	45	>5000	20000		
703	5	1400	20000		
704	30	2600	9800		
705	5	2300	3200		
706	5	2400	5800		
707	180				
708	140				
709	10	2100	14000		
710	110				
711	175				
910	10	3400	3800		
911	9	3500	1900		
912	10	4200	3800		
913	4.5	2400	7000		

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50(nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
914	5.2	2600	2800		
915	11.5	>8000	1900		
918	7		1150		
919	4	2000	4300		
920	16	2100	3000		
921	8.5	1800	3000		
1018	170	4000	5500		9.1
1052	100	2500			16
1053	27	2000	>20000		34
1056	170				17
1075	120	5000	5500		14.5
1095	360	6000			28
1105	250	3500	3000		
1106	75	4000	1700		
1107	65				
1108	22	1400	2600		
1109	80				
1110	45				
1111	18	6050	4400		
1112	3.5	1800	2300		
1113	290				
1114	125				
1115	250				
1116	215				
1117	35	1700	1300		
1118	380				
1119	515				
1120	95				
1121	170				
1122	400				
1123	30	2,400	4500		
1124	270				
1125	55	2300	9000		
2001a			3000		
2100f					
2100g					
2100h			2000		

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
2100i					
2100j	30000		12000		
2100k	520	4000	600		
2100l		750	2200		
2100m					
2100n	670	770	4000		
2100o	670	1150	1500		

We obtained the following data for selected compounds of this invention (Table 18) using the methods described herein (see Examples 1-4). The structures and preparations of compounds of this invention are described in Examples 28-31.

Table 18

Cmpd.	Fluorescent Assay k_{inact} m^{-1} s^{-1}	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
286	370000	300	1600		119
505 b	190000	1500	2100	161	196
505 e	420000	9000	1000		

Example 19

In vivo acute assay for efficacy as anti-inflammatory agent

Results in the Table 19 show that **412f**, **412d** and **696a** inhibit IL-1β production in LPS-challenged mice after oral adminstration using ethanol/PEG/water,

β-cyclodextrin, labrosol/water or cremophor/water as vehicles. The compound was dosed at time of LPS challenge. The protocol is described in Example 7.

Table 19 Inhibition (%) of IL-1β production in LPS-challenged mice.

Compound	10 mg/kg dose	25 mg/kg dose	50 mg/kg dose
412f	17%	25%	32%
412e	5%	17%	61%
696a	0	45%	52%

Example 20
Mouse Carrageenan Peritoneal Inflammation

Inflammation was induced in mice with an intraperitoneal (IP) injection of 10 mg carrageenan in 0.5 ml of saline (Griswold et al., Inflammation, 13, pp. 727-739 (1989)). Drugs are administered by oral gavage in ethanol/PEG/water, β-cyclodextrin, labrosol/water or cremophor/water vehicle. The mice are sacrificed at 4 hours post carrageenan administration, then injected IP with 2 ml of saline containing 5U/ml heparin. After gentle massage of the peritoneum, a small incision is made, the contents collected and volume recorded. Samples are kept on ice until centrifuged (130 x g, 8 mins at 4 °C) to remove cellular material, and the resultant supernatant stored at -20 °C. IL-1β levels in the peritoneal fluid are determined by ELISA.

Results in the Table 20 show prodrug **412f** inhibits IL-1β production in carrageenan-challenged mice after oral adminstration of drug. Compound **214e**

did not inhibit IL-1β production when dosed orally at 50 mg/kg.

Table 20 Inhibition (%) of IL-1β production by **412f** and **412d** in carrageenan-challenged mice.

Dose (mg/kg)	Compound **412f**	Compound **412d**
1	30%	0
10	54%	32%
25	49%	31%
50	73%	36%
100	75%	53%

Example 21
Type II Collagen-induced Arthritis

Type II collagen-induced arthritis was established in male DBA/1J mice at described Wooley and Geiger (Wooley, P.H., Methods in Enzymology, 162, pp. 361-373 (1988) and Geiger, T., Clinical and Experimental Rheumatology, 11, pp. 515-522 (1993)). Chick sternum Type II collagen (4 mg/kg in 10 mM acetic acid) was emulsified with an equal volume of Freund's complete adjuvant (FCA) by repeated passages (400) between two 10 ml glass syringes with a gauge 16 double-hub needle. Mice were immunized by intradermal injection (50 μl; 100μl CII per mouse) of collagen emulsion 21 days later at the contra-lateral side of the tail base. Drugs were administered twice a day (10, 25 and 50 mg/kg) by oral gavage approximately 7 h apart. Vehicles used included ethanol/PEG/water, β-cyclodextrin, labrosol/water or cremophor/water. Drug treatments were initiated within 2 h of the CII booster

immunization. Inflammation was scored on a 1 to 4 scale of increasing severity on the two front paws and the scores are added to give the final score.

Results in the **Figs. 12, 13** and **14** show prodrugs **412f, 412d** and **696a** inhibit inflammation in collagen-induced arthritits in mice after oral adminstration. Compound **214e** did not inhibit inflammation when dosed (50 mg/kg) once a day by oral gavage.

Example 22

In vivo bioavailability determination

The drugs (10-100 mg/kg) were dosed orally to rats (10 mL/kg) in ethanol/PEG/water, β-cyclodextrin, labrosol/water or cremophor/water. Blood samples were drawn from the carotid artery at 0.25, 0.50, 1, 1.5, 2, 3, 4, 6, and 8 hours after dosing, centrifuged to plasma and stored at -70°C until analysis. Aldehyde concentrations were determined using an enzymatic assay. Pharmacokinetic analysis of data was performed by non-linear regression using RStrip (MicroMath Software, UT). Drug availability values were determined as follows: (AUC of drug after oral prodrug dosing/AUC of drug after i.v. dosing of drug)x(dose i.v./dose p.o.) x100%.

Results in Table 21 show that prodrugs **412f**, **412d** and **696a** give significant blood levels of drug and have good drug availability when dosed orally. Blood levels of **214e** were not detected when it was dosed orally.

Table 21 Oral Bioavailability of **412f**, **412d**, **696a** and **214e** in Rat.

Compound	Dose (mg/kg)	Cmax (μg/ml)	Drug Availability (%)
412f	25	2.4	32
412d	25	2.6	35
696a	50	1.2	10
214e	45	0.2	0.9%

Example 23

ICE cleaves and activates pro-IGIF

ICE and ICE homolog expression plasmids

A 0.6 kb cDNA encoding full length murine pro-IGIF (H. Okamura et al., Nature, 378, p. 88 (1995) was ligated into the mammalian expression vector pCDLSRα (Y. Takebe et al., Mol. Cell Biol., 8, p. 466 (1988)).

Generally, plasmids (3 μg) encoding active ICE (above), or the three ICE-related enzymes TX, CPP32, and CMH-1 in the pCDLSRα expression vector (C. Faucheu et al., EMBO, 14, p. 1914 (1995); Y. Gu et al., EMBO, 14, p. 1923 (1995); J. A. Lippke et al., J. Biol. Chem., 271, p. 1825 (1996)), were transfected into subconfluent monolayers of Cos cells in 35-mm dishes using the DEAE-dextran method (Y. Gu et al., EMBO J., 14, p. 1923 (1995)). Twenty-four hours later, cells were lysed and the lysates subjected to SDS-PAGE and immunoblotting using an antiserum specific for IGIF (H. Okamura et al., Nature, 378, p. 88 (1995).

Polymerase chain reaction was used to introduce Nde I sites at the 5' and 3' ends of the murine pro-IGIF cDNA using the following primers: GGAATTCCATATGGCTGCCATGTCAGAAGAC (forward) and GGTTAACCATATGCTAACTTTGATGTAAGTTAGTGAG (reverse). The

resulting NdeI fragment was ligated into E. coli expression vector pET-15B(Novagen) at the NdeI site to create a plasmid that directs the synthesis of a polypeptide of 213 amino acids consisting of a 21-residue peptide (MGSSHHHHHHSSGLVPRGSHM, where LVPRGS represents a thrombin cleavage site) fused in-frame to the N-terminus of pro-IGIF at Ala2, as confirmed by DNA sequencing of the plasmid and by N-terminal sequencing of the expressed proteins. E. coli strain BL21(DE3) carrying the plasmid was induced with 0.8 mM isopropyl-1-thio-β-D-galactopyranoside for 1.5 hours at 37°C, harvested, and lysed by microfluidization (Microfluidic, Watertown, MA) in Buffer A (20 mM sodium phosphate, pH 7.0, 300 mM NaCl, 2 mM dithiothreitol, 10% glycerol, 1 mM phenylmethylsulfonyl fluoride, and 2.5 μg/ml leupeptin). Lysates were cleared by centrifugation at 100,000 x g for 30 min. (His)6-tagged pro-IGIF protein was then purified from the supernatant by Ni-NTA-agarose (Qiagen) chromatography under conditions recommended by the manufacturer.

In Vitro pro-IGIF Cleavage Reactions

In vitro cleavage reactions (30 μl) contained 2 μg of purified pro-IGIF and various concentrations of the purified proteases in a buffer containing 20 mM Hepes, pH 7.2, 0.1% Triton X-100, 2 mM DTT, 1 mM PMSF and 2.5 μg/ml leupeptin and were incubated for 1 hour at 37°C. Conditions for cleavage by granzyme B were as described previously (Y. Gu et al., J. Biol. Chem., 271, p. 10816 (1996)). Cleavage products were analyzed by SDS-PAGE on 16% gels and Coomassie Blue staining, and were subjected to N-terminal amino acid sequencing

using an ABI automated peptide sequencer under conditions recommended by the manufacturer.

Kinetic Parameters of IGIF Cleavage by ICE

The kinetic parameters (k_{cat}/K_M, K_M, and k_{cat}) for IGIF cleavage by ICE were determined as follows. ^{35}S-methionine-labeled pro-IGIF (3000 cpm, prepared by *in vitro* transcription and translation using, the TNT T7-coupled reticulocyte lysate system (Promega) and pro-IGIF cDNA in a pSP73 vector as template) were incubated in reaction mixtures of 60 µl containing 0.1 to 1 nM recombinant ICE and 190 nM to 12 µM of unlabeled pro-IGIF for 8-10 min at 37°C. Cleavage product concentrations were determined by SDS-PAGE and PhosphoImager analyses. The kinetic parameters were calculated by nonlinear regression fitting of the rate vs. concentration data to the Michaelis-Menten equation using the program Enzfitter (Biosoft).

IFN-γ Induction Assays

A.E7 Th1 cells (H. Quill and R. H. Schwartz, J. Immunol., 138, p. 3704 (1987)) (1.3×10^5 cells in 0.15 ml Click's medium supplemented with 10% FBS, 50 µM 2-mercaptoethanol and 50 units/ml IL-2) in 96-well plates were treated with IGIF for 18-20 hours and the culture supernatant were assayed for IFN-γ by ELISA (Endogen, Cambridge, MA).

Example 24

Processing of pro-IGIF by ICE in Cos Cells

Cos cells were transfected with various expression plasmid combinations as described in Example 23. Transfected Cos cells (3.5×10^5 cells in a 35-mm dish) were labeled for 7 hours with 1 ml of methionine-

free DMEM containing 2.5% normal DMEM, 1% dialyzed fetal bovine serum and 300 µCi/ml ^{35}S-methionine (^{35}S-Express Protein Labeling-Mix, New England Nuclear). Cell lysates (prepared in 20 mM Hepes, pH 7.2, 150 mM NaCl, 0.1% Triton X-100, 5 mM N-ethylmaleimide, 1 mM PMSF, 2.5 µg/ml leupeptine) or conditioned medium were immunoprecipitated with an antiIGIF antibody that recognizes both the precursor and the mature forms of IGIF (H. Okamura et al., Nature, 378, p. 88 (1995)). Immunoprecipitated proteins were analyzed by SDS-PAGE (polyacrylamide gel electrophoresis) and fluorography (**Fig. 2A**).

We also measured the presence of IFN-γ inducing activity in the cell lysates and the conditioned media of transfected cells (**Fig. 2B**). Transfected Cos cells (3.5 x 10^5 cells in a 35-mm dish) were grown in 1 ml medium for 18 hours. Media was harvested and used at 1:10 final dilution in the IFN-γ induction assay (Example 23). Cos cell pellets from the same transfection were lysed in 100 µl of 20 mM Hepes, pH 7.0, by freeze-thawing 3 times. Lysates were cleared by centrifugation as described above and were used at a 1:10 dilution in the assay.

Example 25

IGIF is a physiological substrate of ICE

Wild type (ICE+/+) and ICE-/- mice were primed with heat-inactivated *P. acnes*, and Kupffer cells were isolated from these mice 7 days after priming and were then challenged with 1 µg/ml LPS for 3 hours. The amounts of IGIF in the conditioned media were measured by ELISA.

Wild type or ICE-deficient mice were injected intraperitoneally with heat-killed p. acnes as described (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995)). Kupffer cells were prepared seven days later according to Tsutsui et al. (H. Tsutsui et al., Hepato-Gastroenterol., 39, p. 553 (1992)) except a nycodenz gradient was used instead of metrizamide. For each experiment, Kupffer cells from 2-3 animals were pooled and cultured in RPMI 1640 supplemented with 10% fetal calf serum and 1 µg/ml LPS. Cell lysates and conditioned medium were prepared 3 hours later.

Kupffer cells from wild type and ICE-/- mice were metabolically labeled with ^{35}S-methionine as for Cos cells (described above in Example 24) except that methionine-free RPMI 1640 was used in place of DMEM. IGIF immunoprecipitation experiments were performed on cell lysates and conditioned media and immunoprecipitates were analyzed by SDS-PAGE and fluorography as described in Example 23. See **Fig. 3**.

Example 26

Induction of IFN-γ Production In Vivo

LPS mixed with 0.5% carboxymethyl cellulose in PBS, pH 7.4, was administered to mice by intraperitoneal injection (30 mg/kg LPS) in a dose volume of 10 ml/kg. Blood was collected every 3 h for 24 h from groups of three ICE-deficient or wild type mice. Serum IFN-γ levels were determined by ELISA (Endogen).

Example 27

IGIF and IFN-γ Inhibition Assays

Inhibition of IGIF processing by ICE inhibitors was measured in ICE inhibition assays as described herein (see Example 1 and Table 22).

Human PBMC Assays

Human buffy coat cells were obtained from blood donors and peripheral blood mononuclear cells (PBMC) were isolated by centrifugation in LeukoPrep tubes (Becton-Dickinson, Lincoln Park, NJ). PBMC were added (3×10^6/well) to 24 well Corning tissue culture plates and after 1 hr incubation at 37°C, non-adherent cells were removed by gently washing. Adherent mononuclear cells were stimulated with LPS (1 μg/ml) with or without ICE inhibitor in 2 ml RPMI-1640-10% FBS. After 16-18 hr incubation at 37°C, IGIF and IFN-γ were quantitated in culture supernatants by ELISA.

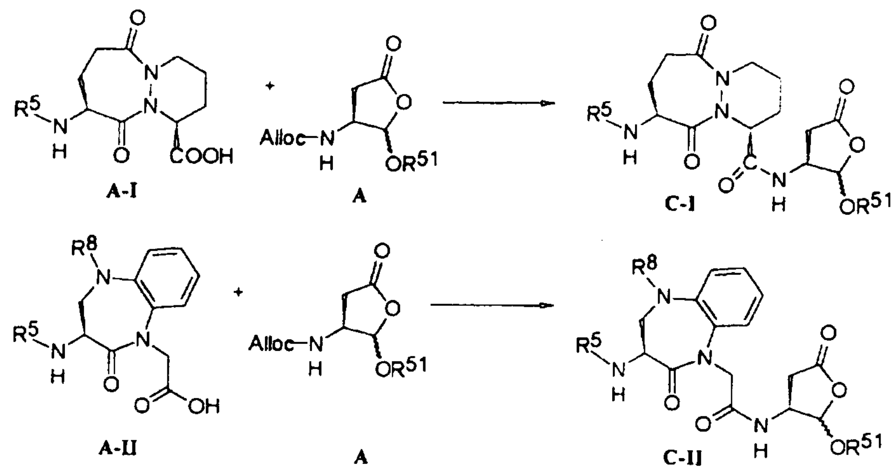
For example, we obtained the following data for compound **412** of this invention using the methods described herein. The structure of compound **412** is shown below.

Table 22

compound	UV-Visible K_i (nM)	Cell PBMC avg. IC50 (nM)
412	1.3	580

Example 28

Compounds of this invention may be prepared via various methods. The following illustrates a preferred method:

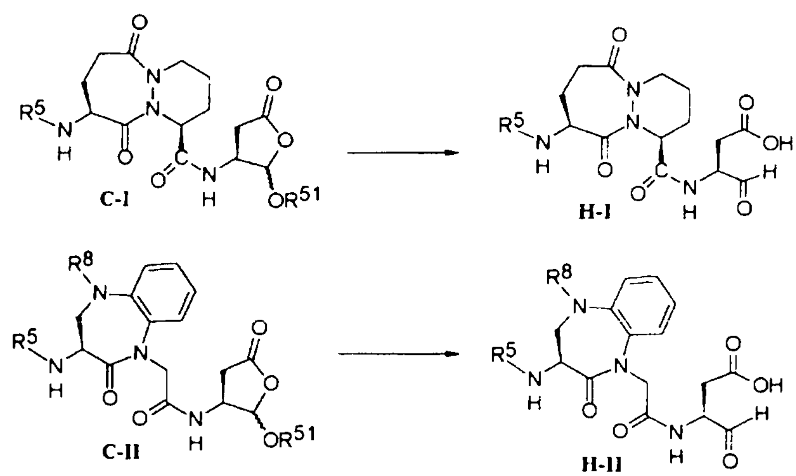


To a solution of **A** (1.1 equivalent) in CH_2Cl_2 (or DMF, or CH_2Cl_2:DMF (1:1)) is added triphenylphosphine (0-0.5 equivalent), a nucleophilic scavenger (2-50 equivalents) and tetrakis-triphenylphosphine palladium(0) (0.05-0.1 equivalent) at ambient temperature under inert atmosphere (nitrogen or argon). After 10 minutes, the above reaction mixture is optionally concentrated, then a solution of acid **A-I** or **A-II** in CH_2Cl_2 (or DMF, or CH_2Cl_2:DMF (1:1)) is added followed by addition of HOBT (1.1 equivalent) and EDC (1.1 equivalent). The resulting reaction mixture is allowed to stir at ambient temperature 1 hour-48 hours to provide coupled products **C-I** or **C-II**.

Various nucleophilic scavengers may be used in the above process. Merzouk and Guibe, Tetrahedron Letters, 33, pp. 477-480 (1992); Guibe and Balavoine, Journal of Organic Chemistry, 52, pp. 4984-4993

(1987)). Preferred nucleophilic scavengers that may be used include: dimedone, morpholine, trimethylsilyl dimethylamine and dimethyl barbituric acid. More preferred nuclophilic scavengers are trimethylsilyl dimethylamine (2-5 equivalents) and dimethyl barbituric (5-50 equivalents). When the nucleophilic scavenger is trimethylsilyl dimethylamine, the above reaction mixture must be concentrated prior to addition of **A-I** or **A-II**.

Other compounds of this invention may be prepared by hydrolyzing compounds represented by **C-I** and **C-II** to compounds represented by **H-I** and **H-II** as described in the following scheme:

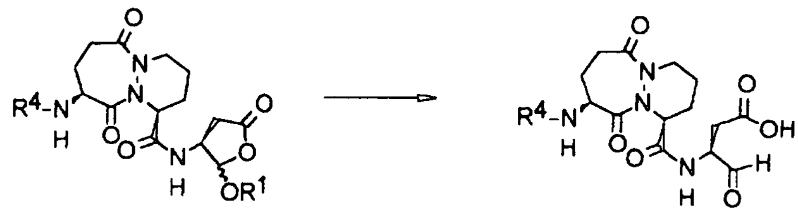


The hydrolysis may be carried out under various conditions, provided that the conditions include an acid and H_2O. Acids that may be used include p-toluensulfonic, methanesulfonic acid, sulfuric, perchloric, trifluoroacetic, and hydrochloric. For example, trifluoroacetic acid (1-90% by weight) or

hydrochloric acid (0.1-30% by weight) in CH_3CN/H_2O (1-90% H_2O by weight) at between 0-50 °C may be used.

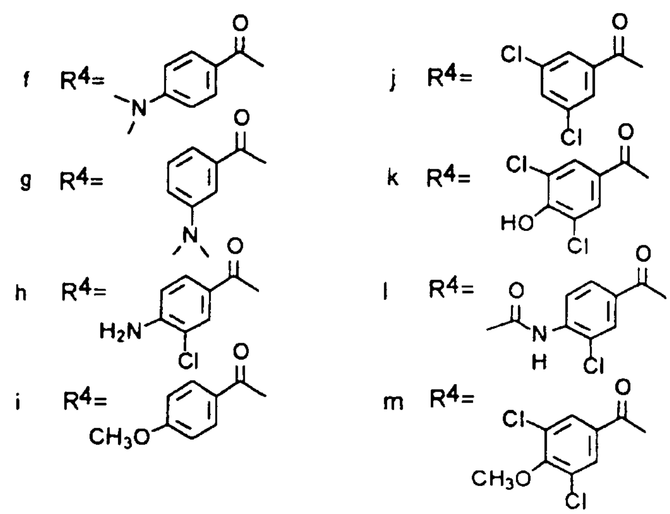
Example 29

Compounds **213f**, **213g**, **213h**, **213i**, **213j**, **213k**, **213l**, **213m**, **214f**, **214g**, **214h**, **214i**, **214j**, **214k**, **214l**, **214m**, **550f**, **550g**, **550h**, **550i**, **550j**, **550k**, **550l** and **550m** were prepared as follows.



213f-m, R^1 = Bn
550f-m, R^1 = Et

214f-m



[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (**213f**), was synthesized from **212f** by the methods used to

prepare **213e** from **212e** to afford 504 mg of **213f** as a yellow solid, ^{1}H NMR (CD_3OD) δ 1.10(br. m, 0.25H), 1.30(br. m, 2H), 1.50(br. m, 1H), 1.65(br. m, 1.5H), 1.80(br. m, 0.25H), 1.90(br. m, 0.25H), 1.95(br. m, 0.5H), 2.05(br. m, 0.25H), 2.15(m, 1H), 2.3(m, 1H), 2.5(br. m, 1H), 2.6(dd, 1H), 2.8(m, 1H), 3.1(br. s, 3H), 3.15(br. m, 1H), 3.32(br. s, 3H), 3.5(m, 1H), 4.5(br. m, 1H), 4.62(d, 0.25H), 4.72(m, 3H), 4.95(m, 1H), 5.1(br. t, 0.25H), 5.15(br. t, 0.75H), 5.7(d, 1H), 6.75(d, 2H), 7.35(br. s, 5H), 7.75(d, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213g), was synthesized from **212g** by the methods used to prepare **213e** from **212e** to afford 400 mg of **213g**, ^{1}H NMR (CD_3OD) δ 1.5(br. m, 1H), 1.65(br. m, 2H), 1.70(br. m, 0.25H), 1.90(br. m, 1H), 1.95(br. m, 1H), 2.05(br. m, 0.25H), 2.10(m, 1H), 2.3(m, 1H), 2.5(m, 2H), 2.59(d, 1H), 2.6(d, 1H), 2.78(d, 1H), 2.8(d, 1H), 2.93(br. s, 4H), 3.05(br. m, 1H), 3.15(br. m, 0.25H), 3.3(br. s, 3H), 3.5(m, 2H), 4.5(br. m, 2H), 4.65(d, 1H), 4.7(br. m, 2H), 4.95(br. m, 1H), 5.15(br. t, 0.25H), 5.2(br. t, 0.75H), 5.2(d, 1H), 6.95(d, 1H), 7.15(d, 1H), 7.25(br. s, 1H), 7.3(br. t, 2H), 7.45(br. s, 6H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-aminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213h), was synthesized from **212h** by the methods used to

prepare **213e** from **212e** to afford 296 mg of **213h**, ^1H NMR ($CDCl_3$) δ 1.55-1.68(m, 1H), 1.7-2.05(m, 3H), 2.3-2.5(m, 2H), 2.65-2.8(m, 1H), 2.85-2.93(m, 1H), 2.95-3.25(m, 3H), 4.44-4.65(m, 2H), 4.68-4.82(m, 1H), 4.9-4.95(d, 1H), 5.05-5.18(m, 2H), 5.28(s, 0.5H), 5.55-5.58(d, 0.5H), 6.52-6.58(d, 0.5H), 6.7-6.76(m, 2H), 6.82-6.85(d, 0.5H), 7.3-7.4(m, 5H), 7.52-7.58(m, 1H), 7.75(s, 0.5H), 7.8(s, 0.5H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213i), was synthesized from **212i** by the methods used to prepare **213e** from **212e** to afford 1.1 g of **213i**, ^1H NMR ($CDCl_3$) δ 1.55-2.05(m, 6H), 2.26-2.5(m, 2H), 2.68-2.82(m, 1H), 2.85-2.92(m, 1H), 2.95-3.25(m, 2H), 3.82(s, 1.5H), 3.85(s, 1.5H), 4.4-4.65(m, 2H), 4.7-4.78(m, 1H), 4.88-4.95(m, 1H), 5.05-5.23(m, 1H), 5.28(s, 0.5H), 5.55-5.58(d, 0.5H), 6.6-6.65(m, 1H), 6.8-6.84(m, 1H), 6.9-6.95(m, 3H), 7.3-7.45(m, 4H), 7.78-7.85(m, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichlorobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213j), was synthesized from **212j** by the methods used to prepare **213e** from **212e** to afford 367 mg of **213j**, ^1H NMR ($CDCl_3$) δ 1.55-2.05(m, 12H), 2.25(d, 1H), 2.35(m, 1H), 2.48(m, 2H), 2.75(m, 2H), 2.9(m, 1H), 2.95-3.25(m, 5H), 4.45(t, 1H), 4.5-4.6(m, 4H), 4.7(m, 1H), 4.75(d, 1H),

4.88(m, 1H), 5.05(m, 2H), 5.15(q, 1H), 5.3(s, 1H), 5.58(d, 1H), 6.5(d, 1H), 6.9(d, 1H), 7.05(d, 1H), 7.25-7.35(m, 5H), 7.6(s, 2H), 7.7(s, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-hydroxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213k), was synthesized from **212k** by the methods used to prepare **213e** from **212e** to afford 593 mg of **213k**, ^1H NMR (CD_3OD) δ 1.5(m, 1H), 1.6-1.7(m, 2H), 1.75-1.95(m,4H), 2.15(m, 2H), 2.3(m, 1H), 2.6(m, 1H), 2.7(m, 1H), 3.05(m, 2H), 3.15(m, 1H), 3.5(m, 2H), 4.45(m, 2H), 4.65(d, 1H), 4.7(m, 1H), 4.95(m, 1H), 5.15(m, 1H), 5.4(s, 1H), 5.7(d, 1H), 7.3(m, 5H), 7.85(s, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-acetamidobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213l), was synthesized from **212l** by the methods used to prepare **213e** from **212e** to afford 133 mg of **213l**, ^1H NMR ($CDCl_3$) δ 1.55-1.7(m, 1H), 1.75-2.05(m, 3H), 2.25(s, 1.5H), 2.27(s, 1.5H), 2.3-2.48(m, 2H), 2.7-2.83(m, 1H), 2.85-2.94(dd, 1H), 2.95-3.25(m, 2H), 4.42-4.65(m, 2H), 4.68-4.85(m, 1H), 4.88-4.95(m, 1H), 5.05-5.18(m, 2H), 5.32(s, 0.5H), 5.55-5.6(d, 0.5H), 6.48-6.55(d, 1H), 6.88-6.92(d, 1H), 7.0-7.04(d, 0.5H), 7.15-7.2(d, 0.5H), 7.3-7.4(m, 4H), 7.64-7.78(m, 2H), 7.88-7.94(m, 1H), 8.45-8.56(m, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-

octahydro-N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213m), was synthesized from **212m** by the methods used to prepare **213e** from **212e** to afford 991 mg of **213m**, ^{1}H NMR ($CDCl_3$) δ 1.5-2.15(m, 5H), 2.2-2.55(m, 3H), 2.6-3.3(m, 4H), 3.95(2s, 3H), 4.45-4.7(m, 2H), 4.7-4.85(m, 1H), 4.8504.95(m, 1H), 5.05-5.25(m, 1H), 5.3(s, 0.5H), 5.6(d, 0.5H), 6.55(d, 0.5H), 6.85(d, 0.5H), 7.0(d, 0.5H), 7.25-7.6(m, 5.5H), 7.75(s, 1H), 7.85(s, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Dimethylaminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550f), was synthesized from **212f** by the methods used to prepare **213e** from **212e** to afford 420 mg of **550f** as an off white solid, ^{1}H NMR ($CDCl_3$) δ 1.2-1.25(br. t, 3H), 1.35(m, 1H), 1.55(br. m, 1H), 1.88-2.02(br. m, 4H), 2.3(d, 1H), 2.35(m, 1H), 2.45(m, 1H), 2.55-2.75(m, 3H), 3.0(s, 6H), 3.25(m, 1H), 3.55(m, 1H), 3.65(m, 1H), 3.75(m, 1H), 3.9(m, 1H), 4.3(t, 1H), 4.55(m, 2H), 4.68(br. m, 1H), 3.9(m, 1H), 4.3(t, 1H), 4.55(m, 2H), 4.68(br. m, 1H), 4.95(br. m, 1H), 5.1(br. m, 2H), 5.45(d, 1H), 6.5(m, 2H), 7.7(m, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-aminobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550h), was synthesized from **212h** by the methods used to prepare **213e** from **212e** to afford 195 mg of **550h** as a white solid, ^{1}H NMR (DMSO-d_6) δ 1.1-1.18(2t, 3H), 1.6-

1.7(m, 2H), 1.88-2.05(m, 2H), 2.1-2.35(m, 3H), 2.48-2.56(m, 1H), 2.75-2.8(m, 0.75H), 2.88-3.08(m, 1.25H), 3.25-3.4(m, 1H), 3.55-3.8(m, 2H), 4.35-4.45(m, 1H), 4.55-4.62(m, 1H), 4.8-4.88(m, 1H), 4.98-5.03(m, 0.25H), 5.1-5.13(m, 0.75H), 5.33(s, 0.25H), 5.58-5.6(d, 0.75H), 5.9-6.0(br. s, 2H), 6.8-6.85(d, 1H), 7.58-7.62(d, 1H), 7.82(s, 1H), 8.22-8.28(d, 1H), 8.48-8.52(d, 0.75H), 8.72-8.76(d, 0.25H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(4-Methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550i), was synthesized from **212i** by the methods used to prepare **213e** from **212e** to afford 135 mg of **550i**, ^{1}H NMR ($CDCl_3$) δ 1.18-1.28(2t, 3H), 1.6-1.75(m, 1.5H), 1.9-2.1(m, 3.5H), 2.22-2.3(d, 0.5H), 2.38-2.47(m, 1.5H), 2.7-2.8(m, 0.5H), 2.8-2.93(m, 1H), 2.94-3.15(m, 1.5H), 3.15-3.28(m, 1H), 3.55-3.62(q, 0.5H), 3.62-3.73(q, 0.5H), 3.78-3.88(q, 0.5H), 3.88(s, 3H), 3.9-3.95(q, 0.5H), 4.33-4.4(m, 0.5H), 4.5-4.55(m, 1H), 4.68-4.76(m, 0.5H), 4.9-4.95(m, 0.5H), 5.1-5.2(m, 1.5H), 5.18(s, 0.5H), 5.48-5.52(d, 0.5H), 6.48-6.55(d, 0.5H), 6.85-6.9(m, 1H), 6.9-6.95(m, 2H), 7.34-7.38(d, 0.5H), 7.78-7.85(m, 2H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-hydroxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550k), was synthesized from **212k** by the methods used to prepare **213e** from **212e** to afford 174 mg of **550k** as a white solid, ^{1}H NMR (DMSO-d_6) δ 1.15(2t, 3H), 1.6-

1.75(m, 2H), 1.9-2.05(m, 2H), 2.1-2.4(m, 5H), 2.5-2.55(m, 1H), 2.7-2.8(m, 0.5H), 2.85-3.0(m, 1H), 3.0-3.1(m, 0.5H), 3.55-3.7(m, 1H), 3.7-3.8(m, 1H), 4.2(t, 0.5H), 4.35-4.45(m, 0.5H), 4.55-4.65(m, 0.5H), 4.8-4.9(m, 0.5H), 5.05(t, 0.5H), 5.15(t, 0.5H), 5.35(s, 0.5H), 5.6(d, 0.5H), 7.95(s, 2H), 8.5(d, 0.5H), 8.65(d, 1H), 8.75(d, 0.5H), 10.9(br. s, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Chloro-4-acetamidobenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550l), was synthesized from **212l** by the methods used to prepare **213e** from **212e** to afford 151 mg of **550l**, ^{1}H NMR ($CDCl_3$) δ 1.2-1.28(2t, 3H), 1.6-1.72(m, 1.5H), 1.88-2.15(m, 3.5H), 2.22-2.28(m, 0.5H), 2.28(s, 3H), 2.38-2.48(m, 1.5H), 2.66-2.92(m, 1.5H), 2.95-3.14(m, 1.5H), 3.2-3.34(m, 1H), 3.56-3.63(q, 0.5H), 3.63-3.72(q, 0.5H), 3.8-3.85(q, 0.5H), 3.9-3.95(q, 0.5H), 4.32-4.38(m, 0.5H), 4.5-4.62(m, 1H), 4.68-4.75(m, 0.5H), 4.88-4.92(m, 0.5H), 5.08-5.2(m, 1.5H), 5.18(s, 0.5H), 5.46-5.5(d, 0.5H), 6.5-6.55(d, 0.5H), 6.98-7.05(m, 1H), 7.42-7.48(d, 0.5H), 7.63-7.78(m, 2.5H), 7.9-7.94(d, 0.5H), 8.44-8.52(m, 1H).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3,5-Dichloro-4-methoxybenzoyl)amino]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550m), was synthesized from **212m** by the methods used to prepare **213e** from **212e** to afford 301 mg of **550m** as a white solid, ^{1}H NMR ($CDCl_3$) δ 1.2-1.35(2t, 3H), 1.5-

1.8(m, 2H), 1.9-2.15(5H), 2.25(d, 0.5H), 2.4-2.5(m, 2H), 2.65-2.8(m, 0.5H), 2..8-3.0(m, 0.5H), 3.0-3.2(m, 1H), 3.2-3.35(m, 0.5H), 3.55-3.65(m, 0.5H), 3.65-3.75(m, 0.5H), 3.8-3.9(m, 0.5H), 3.9-4.0(m, 0.5H), 4.4-4.45(m, 0.5H), 4.55-4.65(m, 0.5H), 4.7-4.8(m, 0.5H), 4.85-4.95(m, 0.5H), 5.05-5.2(m, 0.5H), 5.2(s, 0.5H), 5.5(d, 0.5H), 6.5(d, 0.5H), 6.9(d, 0.5H), 6.95(d, 0.5H), 7.35(d, 0.5H), 7.75(s, 1H), 7.85(s, 1H).

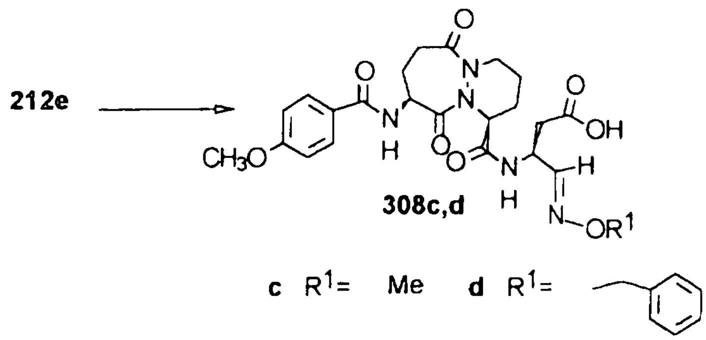
[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichlorobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214j), was synthesized from **213j** by the method used to prepare **2002** from **2001** to afford 62 mg of **214j** as a white solid, ^{1}H NMR (CD_3OD) δ 0.9 (t, 1H), 1.3(br. s, 1H), 1.7(br. m, 1H), 1.9(br. m, 1H), 2.1(br. s, 1H), 2.25(q, 1H), 2.35(m, 1H), 2.48(m, 2H), 2.65(t, 1H), 3.15(br. t, 1H), 3.5(br. m, 1H), 4.3(br. s, 1H), 4.55(m, 2H), 4.95(t, 1H), 5.25(br. s, 1H), 7.6(br. s, 1H), 7.85(br. s, 1H).

[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichloro-4-hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214k), was synthesized from **213k** by the method used to prepare **2002** from **2001** to afford 80 mg of **214k** as a white solid, ^{1}H NMR (CD_3OD) δ 1.6-1.7(m, 1H), 1.8-2.0(m, 2H), 2.0-2.1(m, 2H), 2.15-2.25(m, 1H), 2.3-2.4(m, 1H), 2.4-2.55(m, 2H), 2.6-2.75(m,1H), 3.05-3.2(m, 1H), 3.4-3.6(m, 2H), 4.2-4.3(m, 1H), 4.45-4.6(m, 1H), 4.8-5.0(m, 1H), 5.1-5.2(m, 1H), 7.85(s, 2H).

[3S(1*S*,9*S*)]3-(9-(3-Chloro-4-acetamidobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (2141), was synthesized from **2131** by the method used to prepare **2002** from **2001** to afford 91 mg of **2141** as a white solid, ^{1}H NMR (DMSO-d_6) δ 1.65(br. m, 6H), 1.9(br. m, 6H), 2.15(s, 3H), 2.3(m, 3H), 2.6-2.85(m, 3H), 2.9(m, 2H), 3.0(m, 1H), 4.15(br. q, 1H), 4.4(m, 3H), 5.0(m, 1H), 5.15(m, 1H), 5.45(s, 1H), 7.8(d, 2H), 7.95(d, 1H), 8.05(s, 1H), 8.65(m, 2H), 9.65(s, 1H).

[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichlorobenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214m), was synthesized from **213m** by the method used to prepare **2002** from **2001** to afford 105 mg of **214m** as a white solid, ^{1}H NMR (CD_3OD) δ 1.6-1.75(m, 1H), 1.85-1.95(m, 1H), 2.0-2.1(m, 2H), 2.15-2.25(m, 1H), 2.3-2.4(m, 1H), 2.45-2.55(m, 2H), 2.65-2.75(m, 1H), 3.4-3.55(m, 2H), 3.95(s, 3H), 4.2-4.3(m, 1H), 4.45-4.6(m, 1H), 4.9-5.0(m, 1H), 5.15-5.2(m, 1H), 7.9(s, 2H).

Compounds **308c** and **308d** were prepared as follows.

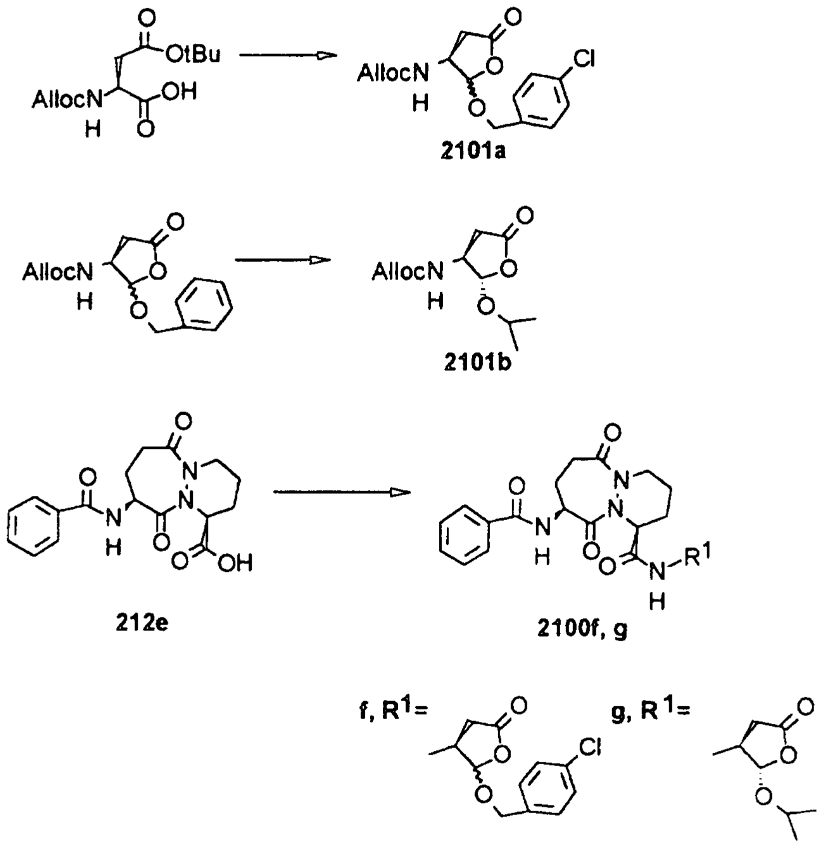


[3*S*(1*S*,9*S*) 3-(9-(4-Methoxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-amino]-4-oxobutanoic acid, O-methyl oxime (308c), was synthesized from **212e** via the methods used to prepare **308b** from **212e** to afford 266 mg of **308c** ^{1}H NMR ($CDCl_3$) δ 1.6-1.7(m, 1H), 1.88-1.98(m, 3H), 2.02-2.15(m, 1H), 2.3-2.4(m, 1H), 2.65-2.95(m, 3H), 3.04-3.09(m, 1H), 3.12-3.25(m, 1H), 3.84(s, 3H), 3.86(s, 3H), 4.5-4.58(m, 1H), 4.88-4.95(m, 1H), 5.1-5.25(m, 2H), 6.86-6.9(d, 2H), 7.15-7.25(m, 2H), 7.36-7.4(m, 1H), 7.75-7.8(d, 2H).

[3*S*(1*S*,9*S*) 3-(9-(4-Methoxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-amino]-4-oxobutanoic acid, O-benzyl oxime (308d), was synthesized from **212e** via the methods used to prepare **308b** from **212e** to afford 270 mg of **308d**, ^{1}H NMR ($CDCl_3$) δ 1.55-1.65(m, 1H), 1.8-2.1(m, 4H), 2.3-2.4(m, 1H), 2.65-2.88(m, 3H), 2.9-3.3(m, 3H), 4.5-4.58(m, 1H), 4.88-4.95(m, 1H), 5.05(s, 2H), 5.1-5.2(m, 1H), 6.82-

6.95(m, 2H), 7.02-7.15(m, 2H), 7.28(m, 5H), 7.45(m, 1H), 7.72(d, 2H).

Compounds **2100f, 2100g, 2100h, 2100i** and **2100j** were prepared as described below.



(3*S*,2*RS*) 3-Allyloxycarbonylamino-2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran (2101a), was synthesized from allyloxycarbonylamino-β-*tert*-butyl aspartate by the methods employed by Chapman (<u>Bioorg. & Med. Chem. Lett.</u>, 2, pp.615-618 (1992)) to prepare (3*S*,2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran

using 4-chlorobenzyl alcohol instead of benzyl alcohol to afford 1.84 g of **2101a** as a crystalline solid.

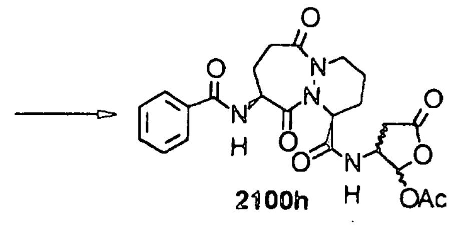
[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-(4-chlorobenzyl)oxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100f), was synthesized from **212e** by the methods used to prepare **213e** from **212e** using **2101a** to afford 380 mg of **2100f**, ^{1}H NMR ($CDCl_3$) δ 1.8-2.0(m, 10H), 2.30(d, 1H), 2.31-2.5(m, 3H), 2.7-2.9(m, 3H), 3.05(m, 2H), 3.1-3.2(m, 4H), 4.45(q, 1H), 4.5-4.6(m, 3H), 4.7(d, 2H), 4.85(d, 1H), 4.9(t, 1H), 5.2(t, 1H), 5.15(m, 2H), 5.25(s, 1H), 5.55(d, 1H), 6.5(d, 1H), 6.9(d, 1H), 6.95(d, 1H), 7.25(m, 3H), 7.35(t, 2H), 7.45(m, 2H), 7.55(1H), 7.8(m, 3H).

(3*S*,2*RS*) 3-Allyloxycarbonylamino-2-*anti*-isopropoxy-5-oxotetrahydrofuran (2101b), was synthesized from (3*S*,2*RS*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran via the method used to prepare **2100d** from **214e** using H_2SO_4 instead of pTSA to afford **2101b**.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-*anti*-isopropoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100g), was synthesized from **212e** by the methods used to prepare **213e** from **212e** using **2101b** to afford 31 mg of **2100g**, ^{1}H NMR ($CDCl_3$) δ 1.19 (d), 1.94 (br s), 2.00-2.12 (m), 2.24 (d), 2,42 (dd), 2.71-2.83 (m), 3.02 (dd), 3.12-3.27 (overlapping m), 3.93 (m), 4.32-4.37 (m,),

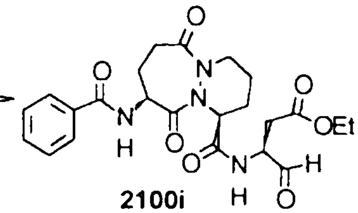
4.52-4.63 (m), 4.90-4.95 (m), 5.12-5.20 (m), 5.28 (s), 6.93 (d), 7.10 (d), 7.41-7.50 (m), 7.51-7.58 (m), 7,84 (d).

214e



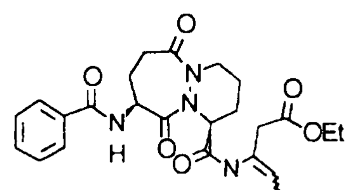
2100h

[1*S*,9*S*(2*RS*,3*RS*)] 9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-N-(2-acetoxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100h). A solution of **214e** (287 mg, 0.65 mmol) in pyridine (5 mL) was treated with Ac_2O (0.4 mL, 3.62 mmol). After 6 hours, the reaction mixture was poured into 5% $NaHSO_4$ and extracted 3 times with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (SiO_2, EtOAc) afforded 119 mg of **2100h**, ^{1}HNMR ($CDCl_3$, mixture of four diastereoisomers) δ 1.80-2.05(m), 2.12(s), 2.13(s), 2.19(s), 2.22(d), 2.67-2.75(m), 2.80-2.95(m), 3.00-3.20(m), 3.21-3.33(m), 3.50-3.95(four discrete multiplets), 4.19(m), 4.55(m), 4.57-4.65(m), 4.69(m), 4.85-4.95(m), 5.04(m), 5.10(s), 5.10-5.22(m), 6.46(d), 6.03(s), 6.50(d), 6.58(d), 6.75(d), 6.95-7.05(m), 7.22(m), 7.30(m), 7.71(d), 7.75-7.83(m).

2100b ⟶ 

2100i

[3*S*(1*S*,9*S*)]3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid ethyl ester (2100i). To a solution of **2100b** (1.5 g, 2.7 mmol) in CH_3CN (10 mL) was added 1N HCl at ambient temperature. After 6 hours solid $NaHCO_3$ was added and the product extracted with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography (SiO_2, 30-100% CH_2Cl_2 in EtOAc) afforded 123 mg of **2100i**, ^{1}H NMR ($CDCl_3$) δ 1.25(t, 3H), 1.6-1.8(m, 1H), 1.9-2.2(m, 5H), 2.4-2.5(m, 1H), 2.75-2.9(m, 2H), 3.0-3.1(m, 2H), 3.2-3.25(m, 1H), 4.05-4.2(m, 1H), 4.5-4.7(m, 1H), 5.1-5.25(m, 1H), 7.0-7.2(m, 2H), 7.4-7.45(m, 2H), 7.5(t, 1H), 7.8(t, 2H), 9.5(s, 1H).

2100i ⟶ 

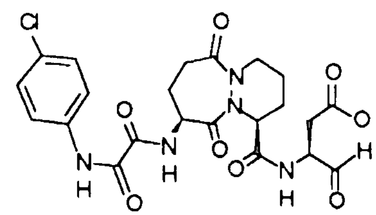
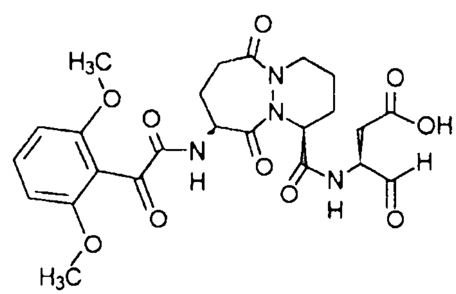
2100j

[3*S*(1*S*,9*S*)]3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-acetoxy-3-butenoic acid ethyl ester (2100j), was synthesized from **2100i** via the method used to prepare

2100h from **214e** to afford 347 mg of **2100j**, ^{1}H NMR ($CDCl_3$) δ 1.3(t, 3H), 1.6-1.8(m, 2H), 1.9-2.25(m, 4H), 2.25(s, 3H), 2.3-2.45(m, 1H), 2.8-3.0(m, 1H), 3.0-3.25(m, 2H), 3.4-3.45(m, 2H), 4.1-4.2(m, 2H), 4.55-4.7(m, 1H), 5.1-5.25(m, 1H), 6.8(s, 1H), 7.0-7.1(m, 2H), 7.5(t, 1H), 7.8(t, 2H), 9.5(s, 1H).

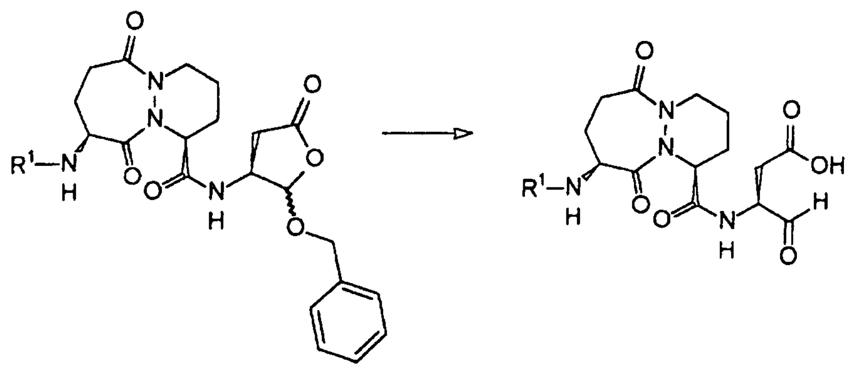
Compounds **500** and **501** are described in Table 23. These compounds were prepared by methods similar to the methods used to prepare compounds **404-449** (see, Example 11).

Table 23

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+H)+
500		C22H24ClN5O8	521.92	11.448 (A) 0.991	523.1
501		C24H28N4O10	532.51	10.13 0.97	533

The compounds described below (**213m, 213n, 213o, 213p, 213q, 213r, 213s, 213t, 213u, 213v, 213w, 213x,** and **214w**), were prepared by methods similar to the methods used to prepare compounds **213b-f**.

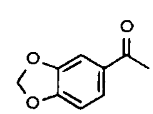
Compounds **419, 415, 450, 456, 475, 404, 486, 487, 417, 408** and **418** may also be prepared as described below.

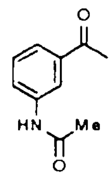
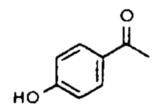
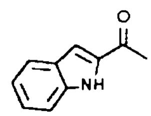
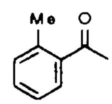
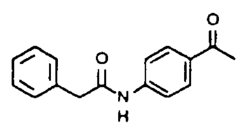
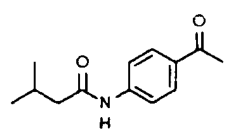
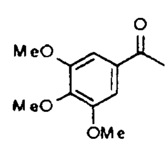


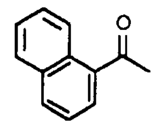
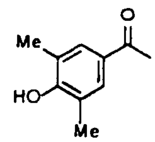
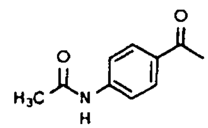
213m-x
214w, 404, 408, 415,

417, 418, 419, 450,

456, 475, 486, 487

compound	R^1
213m, 419	MeOC(O)-
213n, 415	

213o, 450	
213p, 456	
213q, 475	
213r, 404	
213s, 486	
213t, 487	
213u, 417	

213v, 408	
213w, 214w	
213x, 418	

[1*S*,9S(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213n), was isolated as a mixture of diastereomers (syn:anti isomer ratio 6:4) (1.43g, 82%) as a white solid: mp. 206-10°C; IR (KBr) 3288, 1787, 1680, 1657, 1651, 1619, 1548, 1440, 1256, 1135; ^{1}H NMR (D_6-DMSO) δ 8.75 (0.4H, d), 8.55 (0.6H, d), 8.45 and 8.43 (1H, 2 x d), 7.50 (1H, d), 7.42 (1H, s), 7.40-7.27 (5H, m), 7.01 (1H, d), 6.11 (2H, s), 5.67 (0.6H, d), 5.43 (0.4H, s), 5.10-5.00 (1H, m), 4.90-4.59 (3.5H, m), 4.45-4.25 (1.5H, m), 3.47-3.20 (1H, m), 3.20-2.70 (2H, m), 2.65-2.35 (1H, m), 2.35-2.00 (3H, m), 2.00-1.75 (2H, m), 1.65-1.40 (2H, m). Anal. Calcd for $C_{29}H_{30}N_4O_9$: C, 60.20; H, 5.23; N, 9.68. Found: C, 60.08; H, 5.32; N, 9.50. MS (ES$^+$)

580 (M^+ + 2, 35%), 579 (M^+ + 1, 100), 404 (5), 367 (5), 236 (7), 107 (5).

[1*S*,9*S*(2*RS*,3*S*)]9-[(3-Acetamido)benzamido]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213o), anti-isomer as a white foamy solid (0.73g, 69%): mp. 135-40°C; $[\alpha]_D^{21}$ -37.3° (c 0.1, CH_2Cl_2); IR (KBr) 3452, 3310, 1790, 1664, 1659, 1650, 1549, 1425, 1258, 1121; ^1H NMR (D_6-DMSO) δ 10.11 (1H, s), 8.77 (1H, d), 8.57 (1H, d), 8.01 (1H, s), 7.76 (1H, d), 7.55 (1H, d), 7.45-7.25 (6H, m), 5.43 (1H, s), 5.08-5.00 (1H, m), 4.95-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.45-2.06 (4H, m), 2.06 (3H, s), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m). Anal. Calcd for $C_{30}H_{33}N_5O_8 \cdot 0.75H_2O$: C, 59.54; H, 5.75; N, 11.57. Found: C, 59.40; H, 5.62; N, 11.50. MS (ES^+) 593 (M^+ + 2, 33%), 592 (M^+ + 1, 100), 574 (7), 487 (7), 475 (6), 385 (9), 373 (26), 318 (14), 296 (11), 266 (10), 221 (22).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(4-hydroxybenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213p), was isolated as a foam (1.2g, 77%): $[\alpha]_D^{20}$ -115° (c 0.20, CH_2Cl_2); IR (KBr) 3368, 2946, 1794, 1654, 1609, 1540, 1505, 1421, 1277, 1175, 1119, 980; ^1H NMR (D_6-DMSO) δ 10.1 (1H, s), 8.80 (0.5H, d, J = 6.6), 8.60 (0.5H, d, J = 7.2), 8.40-8.36 (1H, 2d), 7.82 (2H, d, J = 8.0), 7.41 (5H, bs), 6.86 (2H, d, J 8.6), 5.72 (0.5H,

d, J = 5.0), 5.49 (0.5H, bs), 5.13-5.07 (1H, m), 4.95-4.65 (2.5H, m), 4.49-4.38 (2.5H, m), 3.49-3.30 (2H, m), 3.21, 2.79 (2H, m), 2.40-1.41 (7H, m). MS (ES^+) 551.

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(indol-2-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213q), was isolated as a white glassy solid (80%): mp. 145-149°C; $[\alpha]_D^{23}$ -56.0° (c 0.05, CH_2Cl_2); IR (KBr) 3399-3319, 1791, 1657, 1543, 1420, 1253, 1119; ^1H NMR ($CDCl_3$) δ 9.54 (1H, s), 7.65 (1H, d, J = 7.9), 7.51 (1H, d, J = 6.9), 7.44-7.25 (7H, m), 7.18-7.06 (3H, m), 5.30-5.20 (1H, m), 5.27 (1H, s), 4.84 (1H, m), 4.79 (1H, d, J = 11.4), 4.56 (1H, d, J = 11.3), 4.47 (2H, m), 3.28 (1H, m), 3.10-2.97 (2H, m), 2.71 (1H, m), 2.47-2.37 (1H, m), 2.26 (1H, d, J = 17.9), 2.09 (1H, m), 1.83, 1.70, 1.51 (4H, 3m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(2-toluoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213r), was isolated as a mixture of diastereomers (syn:anti isomer ratio 55:45) as a white foamy solid (1.46g, 89%): mp. 106-10°C; IR (KBr) 3306, 2947, 1791, 1659, 1650, 1535, 1421, 1256, 1122; ^1H NMR (D_6-DMSO) δ 8.76 (0.45H, d), 8.56 (0.55H, d), 8.49 and 8.47 (1H, 2 x d), 7.41-7.19 (9H, m), 5.67 (0.55H, d), 5.43 (0.45H, s), 5.11-5.02 (1H, m), 4.86-4.55 (3.5H, m), 4.45-4.25 (1.5H, m), 3.40-3.20 (1H, m), 3.20-2.70 (2H, m), 2.65-2.40 (1H, m), 2.34 (3H, s), 2.30-1.70 (5H, m), 1.65-1.40 (2H, m). Anal. Calcd for $C_{29}H_{32}N_4O_7$: C, 62.66; H, 5.95; N, 10.08. Found: C, 62.91; H, 6.00;

N, 9.70. MS (ES^+) 550 (M^+ + 2, 43%), 549 (M^+ + 1, 100), 374 (3), 280 (4), 279 (20), 118 (5).

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-[4-(phenylacetamido)benzamido]-6H-pyridazino[1,2-a][1,2]diazepin-1-carboxamide (213s), was isolated as the anti-isomer as a white foamy solid (0.64g, 77%): mp. 137-41°C; $[\alpha]_D^{21}$ -48.2° (c 0.05, CH_3OH); IR (KBr) 3477, 3314, 1791, 1659, 1599, 1529, 1499, 1406, 1256, 1122; ^1H NMR (D_6-DMSO) δ 10.45 (1H, s), 8.76 (1H, d), 8.50 (1H, d), 7.86 (2H, d), 7.69 (2H, d), 7.41-7.20 (10H, m), 5.43 (1H, s), 5.08-4.98 (1H, m), 4.90-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.67 (2H, s), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.39 (1H, dd), 2.30-2.00 (3H, m), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m). Anal. Calcd for $C_{36}H_{37}N_5O_8 \cdot 0.5H_2O$: C, 63.90; H, 5.66; N, 10.35. Found: C, 63.68; H, 5.67; N, 10.24. MS (ES^+) 669 (M^+ + 2, 40%), 668 (M^+ + 1, 100), 640 (12), 435 (18), 425 (23), 403 (33), 328 (17), 302, (32), 274 (22), 197 (16), 138 (17).

[1*S*,9*S*(2*RS*,3*S*)]N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-[4-(3-methylbutan-1-oylamino)benzamido]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213t), was isolated as a white foamy solid (0.63g, 80%): mp. 159-64°C; $[\alpha]_D^{21}$ -37.0° (c 0.05, CH_3OH); IR (KBr) 3463, 3321, 1790, 1680, 1658, 1650, 1644, 1595, 1525, 1501, 1408, 1251, 1113, 933; ^1H NMR (D_6-DMSO) δ 10.13 (1H, s), 8.76 (1H, d), 8.48 (1H, d), 7.85 (2H, d), 7.68 (2H, d),

7.40-7.25 (5H, m), 5.43 (1H, s), 5.08-4.95 (1H, m), 4.92-4.73 (1H, m), 4.76 and 4.68 (2H, dd), 3.40-3.20 (1H, m), 3.09 (1H, dd), 3.02-2.75 (1H, m), 2.39 (1H, dd), 2.35-2.00 (6H, m), 2.00-1.75 (2H, m), 1.70-1.40 (2H, m), 0.93 (6H, d). Anal. Calcd for $C_{33}H_{39}N_5O_8 \cdot 0.5H_2O$: C, 61.67; H, 6.27; N, 10.90. Found: C, 61.49; H, 6.24; N, 10.86. MS (ES^+) 635 (M^+ + 2, 39%), 634 (M+ + 1, 100), 484 (10), 427 (9), 274 (18), 268 (37), 204 (19), 117 (13).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(3,4,5-trimethoxybenzoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213u), was isolated as a white solid (81%): mp. 120-132°C; IR (KBr) 3361-3334, 1792, 1659, 1585, 1536, 1499, 1457, 1416, 1340, 1236, 1126, 989; ^{1}H NMR ($CDCl_3$) δ 7.39-7.29 (6H, m), 7.12 (1H, s), 7.03 (1H, s), 6.92, 6.83, 6.48 (approx 3H, 3d, J = 8.1, 7.5, 8.1), 5.57 (d, J = 5.3), 5.27 (1H, s), 5.23-5.06, 4.91-4.71, 4.64-4.43, (6H, 3m), 3.92, 3.91, 3.89, 3.88 (9H, 4s), 3.32-2.70, 2.52-2.08, 1.91, 1.63 (1H, 4m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(naphth-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213v), was isolated as a white solid (78%): mp. 121-7°C; IR (KBr) 3534-3331, 1791, 1659, 1528, 1420, 1256, 1122; ^{1}H NMR ($CDCl_3$) δ 8.34-8.29 (1H, m), 7.98-7.87 (2H, m), 7.68-7.45 (4H, m), 7.34-7.24 (5H, m), 7.04 (d, J = 6.8), 6.78 (d, J = 7.8), 6.66 (d, J = 7.7), 6.48 (2H, d, J = 7.5)5.56 (d, J = 5.4), 5.15

(1H, s), 5.30-5.14, 5.0, 4.89 (d, J = 11.2), 4.71-4.41 (6H), 3.18-2.80, 2.50-2.27, 2.08-1.60 (11H, 3m).

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(4-hydroxy-3,5-dimethylbenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213w), was isolated as a mixture of diastereoisomers (65/35) as a white solid (0.9g, 65%): mp. 110-115°C (decomp.); IR (KBr) 3409, 2945, 1792, 1658, 1606, 1534, 1486, 1420, 1330, 1276, 1209, 1122, 980, 960; ^{1}H NMR ($CDCl_3$) δ 7.66 (0.35H, d, J = 6.9), 7.46-7.20 (7H, m), 6.93 (0.35H, d, J = 7.7), 6.85 (0.65H, d, J = 7.6), 6.73 (0.65H, d, J = 7.6), 5.96 (0.35H, bs), 5.85 (0.65H, bs), 5.56 (0.65H, d, J = 5.2), 5.28 (0.35H, bs), 5.20-4.98 (2H, m), 4.96-4.40 (4H, m), 3.28-2.55 (3H, m), 2.53-2.32 (1H, m), 2.23 (6H, 2s), 2.03-1.40 (7H, m). MS (ES^-) 577, (ES^+) 579.

[1*S*,9*S*(2R*S*,3*S*)] 9-[4-(Acetylamino)benzoylamino]-N-(2-benzyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboximide (213x), was isolated as a colourless poweder (691mg, 86%): mp. 150-70°C; $[\alpha]_D^{22}$ -10.1° (c 0.10, Me_2CO); IR (KBr) 3313, 1791, 1679, 1654, 1597, 1528, 1501, 1457, 1407, 1371, 1315, 1255, 1184, 1122, 933; ^{1}H NMR (d6-DMSO) δ 8.75 (1H, d), 8.47 (1H, d), 7.84 (2H, d), 7.66 (2H, d), 7.35 (5H, m), 5.43 (1H, s), 5.06-5.00 (1H, m), 4.90-4.64 (3H, m), 4.46-4.26 (2H, m), 3.16-2.86 (2H, m), 2.45-2.05 (5H, m), 2.07 (3H, s), 2.00-1.84 (2H, m), 1.68-1.56 (2H, m); Anal. Calcd for $C_{30}H_{33}N_5O_8 \cdot H_2O$: C, 59.11; H, 5.79; N,

11.49. Found: C, 59.38; H, 5.66; N, 11.31; M.S. (ES^+) 614 (100%), 592 (M^++1.66).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (415), was prepared by a similar method as compound **214e** to afford a white solid (297mg, 84%): mp. 158-62°C; $[\alpha]_D^{24}$ -109.5° (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 1783,1659, 1650, 1538, 1486, 1439, 1257, 1037; ^1H NMR (CD_3OD) δ 7.48 (1H, dd), 7.35 (1H, d), 6.88 (1H, d), 6.03 (2H, s), 5.25-5.15 (1H, m), 5.02-4.90 (1H, m), 4.63-4.45 (2H, m), 4.30-4.20 (1H, m), 3.57-3.30 (1H, m), 3.20-3.05 (1H, m), 2.75-2.10 (5H, m), 2.10-1.60 (4H, m). MS (ES^+) 488 (M+, 25%), 487 (M^+ - 1, 100), 443 (8), 387 (3), 315 (5), 150 (6), 127 (5), 113 (8). Accurate mass calculated for $C_{22}H_{25}N_4O_9$ (MH^+): 489.1621. Found 489.1648.

[3*S*(1*S*,9*S*)] 3-{9-[(3-Acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (450), was prepared by a similar method as compound **214e** to afford a white foamy solid (378mg, 94%): mp. 175-9°C; $[\alpha]_D^{22}$ -91.7° (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3319, 1659, 1590, 1553, 1427, 1260; ^1H NMR (CD_3OD) δ 8.01 (1H, d), 7.74 (1H, dd), 7.56 (1H, d), 7.45-7.35 (1H, m), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.60-4.45 (2H, m), 4.30-4.20 (1H, m), 3.55-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-2.20 (5H, m), 2.14 (3H, s), 2.20-1.60 (4H). Anal. Calcd for $C_{23}H_{27}N_5O_8 \cdot 1.5H_2O$: C, 52.27; H, 5.72; N, 13.25. Found:

C, 52.31; H, 5.86; N, 12.85. MS (ES^+) 501 (M+, 26%), 500 (M^+ - 1, 100), 328 (2), 149 (3), 113 (3).

[3*S*(1*S*,9*S*)] 3-[4-(Hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (456), was prepared by a similar method as compound **214e** to afford a white solid (0.73g, 72%): mp. >260°C; $[\alpha]_D^{20}$ -66° (c 0.34, MeOH); IR (KBr) 3401, 2946, 1651, 1609, 1584, 1506, 1426, 1277, 1257, 1177; ^{1}H NMR (D_6-DMSO) δ 10.2 (1H, very bs), 9.17 (1H, bs), 8.65 (1H, s), 8.37 (1H, d, J 5.4), 7.81 (2H, d, J = 8.2), 6.87 (2H, d, J = 8.4), 5.24 (1H, m), 4.92-4.86 (1H, m), 4.41-4.32 (2H, m), 3.68-3.21 (3H, m), 3.12-2.79 (1H, m), 2.50-1.42 (7H, m). MS (ES^+) 459.

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(indol-2-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (475), was prepared by a similar method to that described for compound **214e** to afford a white solid (79%): mp. 150°C (softens) 190-210°C; $[\alpha]_D^{23}$ -97.5° (c 0.1, CH_3OH); IR (KBr) 3319, 1658, 1650, 1549, 1421, 1256; ^{1}H NMR (CD_3OD) δ 7.61 (1H, d, J = 8.0), 7.43 (1H, d, J = 8.1), 7.21 (2H, m), 7.05 (1H, m), 5.21 (1H, m), 5.07-4.77 (1H, m), 4.54 (2H, m), 4.23 (1H, m), 3.46 (1H, m), 3.14 (1H, m), 2.66-1.71 (9H, m). MS (ES^+, m/z), 482 (M^+ - 1, 100%).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(2-toluoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (404), was prepared by

a similar method as compound **214e** to afford a white solid (0.79g, 86%): mp. 156-9°C; $[\alpha]_D^{25}$ -119.7° (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3387, 3309, 2956, 1785, 1659, 1650, 1535, 1422, 1278; ^1H NMR (CD_3OD) δ 7.46-7.15 (4H, m), 5.25-5.15 (1H, m), 5.02-4.90 (1H, m), 4.58-4.45 (2H, m), 4.30-4.20 (1H, m), 3.55-3.30 (1H, m), 3.20-3.05 (1H, m), 2.80-2.20 (4H, m), 2.41 (3H, s), 2.20-1.60 (5H, m). MS (ES^+) 458 (M+, 27%), 457 (M^+ - 1, 100), 413 (13), 339 (8), 285 (5), 134 (6), 127 (11). Accurate mass calculated for $C_{22}H_{27}N_4O_7$ (MH^+): 459.1880. Found 459.1854.

[3*S*(1*S*,9*S*)] 3-{6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-[4-(phenylacetamido)benzamido]-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (486), was prepared by a similar method as compound **214e** to afford a white solid (325mg, 89%): mp. 165-9°C; $[\alpha]_D^{22}$ -69.1° (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3318, 1658, 1599, 1530, 1505, 1407, 1258; ^1H NMR (CD_3OD) δ 7.85 (2H, d), 7.69 (2H, d), 7.38-7.20(5H, m), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.57-4.45 (2H, m), 4.30-4.20 (1H, m), 3.70 (2H, s), 3.55-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-1.60 (9H, m). Anal. Calcd for $C_{29}H_{31}N_5O_8 \cdot 1.5H_2O$: C, 57.61; H, 5.67; N, 11.58. Found: C, 57.81; H, 5.74; N, 11.47. MS (ES^+) 577 (M+, 33%), 576 (M^+ - 1, 100), 502 (2).

[3*S*(1*S*,9*S*)] 3-{6,10-Dioxo-9-[4-(3-methylbutan-1-oylamino)benzamido]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido}-4-oxobutanoic acid (487), was prepared by a similar

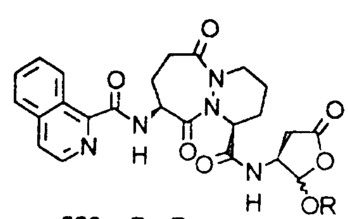
method as compound **214e** to afford a white foamy solid (335mg, 93%): mp. 176-80°C; $[\alpha]_D^{22}$ -88.0° (c0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3321, 2960, 1781, 1660, 1597, 1529, 1407, 1258, 1187; ^1H NMR (CD_3OD) δ 7.86 (2H, d), 7.69 (2H, d), 5.25-5.15 (1H, m), 5.05-4.90 (1H, m), 4.60-4.45 (2H, m), 4.30-4.20 (1H, m), 3.57-3.30 (1H, m), 3.20-3.00 (1H, m), 2.75-1.60 (12H, m), 1.00 (6H, d). Anal. Calcd for $C_{26}H_{33}N_5O_8 \cdot H_2O$: C, 55.61; H, 6.28; N, 12.45. Found: C, 56.00; H, 6.37; N, 12.15. MS (ES^+) 543 (M+, 31%), 542 (M^+ - 1, 100), 498 (2), 468 (3).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(3,4,5-trimethoxybenzoylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (417), was prepared by a similar method to that described for compound **214e** to afford a white solid (0.63g, 92%): mp. 145-155°C (approx., not sharp); $[\alpha]_D^{27}$ -114.6° (c 0.11, CH_3OH); IR (KBr) 3327, 1658, 1586, 1548, 1501, 1416, 1341, 1238, 1126; ^1H NMR (CD_3OD) δ 7.22 (2H, s), 5.21 (1H, m), 5.00 (1H, m), 4.56, 4.49 (2H, 2m), 4.25 (1H, m), 3.88 (6H, s), 3.80 (3H, s), 3.55-3.43 (1H, m), 3.12 (1H, m), 2.71-1.70 (9H, m). Anal. Calcd for $C_{24}H_{30}N_4O_{10} \cdot 2H_2O$: C, 50.52; H, 6.01; N, 9.82. Found: C, 50.49; H, 6.05; N, 9.68. MS (ES^+, m/z) 533 (M^+ - 1, 100%).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(naphth-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (408), was prepared by a similar method to that described for compound **214e** to afford a

white solid (73%): mp. 157-165°C (not sharp); $[\alpha]_D^{27}$ -140.5° (c 0.1, CH_3OH); IR (KBr) 3325, 1658, 1531, 1420, 1278, 1257; ^1H NMR (CD_3OD) δ 8.33-8.28 (1H, m), 8.01-7.78 (2H, m), 7.71 (1H, d, J = 6.0), 7.59-7.52 (3H, m), 5.27 (1H, m), 5.12-5.03 (1H, m), 4.55 (2H, m), 4.25 (1H, m), 3.64-3.43 (1H, m), 3.24-3.12 (1H, m), 2.80-1.67 (9H, m). Anal. Calcd for $C_{25}H_{26}N_4O_7 \cdot 2H_2O$: C, 56.60; H, 5.70; N, 10.56. Found: C, 56.70; H, 5.80; N, 10.33. MS (ES^+, m/z), 493 (M^+ - 1, 100%).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-4-(hydroxy-3,5-dimethylbenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (214w), was prepared by a similar method as compound **214e** to afford 210mg (62%) of a white solid: mp. >260°C; $[\alpha]_D^{20}$ -93° (c 0.20, MeOH); IR (KBr) 3401, 2948, 1651, 1604, 1559, 1486, 1421, 1325, 1276, 1210; ^1H NMR (D_6-DMSO) δ 9.39 (1H, bs), 8.29 (1H, d, J = 5.9), 7.55 (2H, s), 6.64 (1H, d, J = 6.1), 5.79 (1H, s), 5.25-5.21 (1H, m), 1.90-1.82 (1H, m), 4.41-3.69 (2H, m), 3.47-3.20 (3H, m), 2.97-2.91 (1H, m), 2.23 (6H, s), 2.25-1.60 (7H, m).



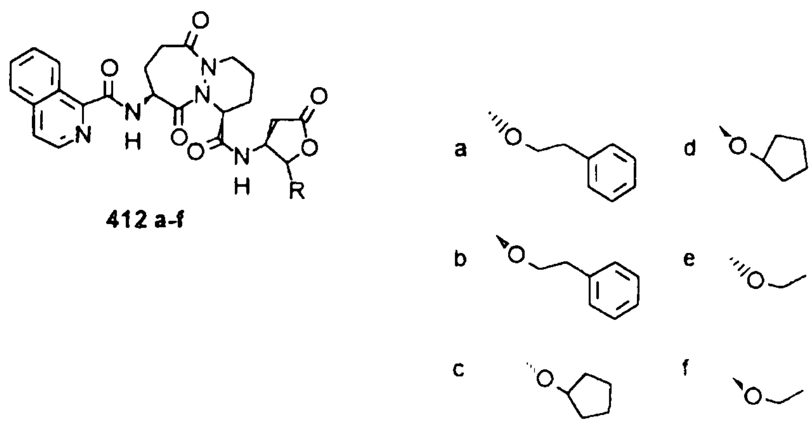
550q R= Et

213y R= Bn

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-

octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550q), was synthesized via methods used to prepare 213e to afford 550q.

[1*S*,9*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (213y), was synthesized via methods used to prepare 213e to afford 213y.



412 a-f

[1*S*,9*S*(2*S*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (412a) was synthesized via methods used to prepare 550q using 513a-1 to afford 412a.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (412b) was synthesized via

methods used to prepare **550q** using **513a-2** to afford **412b**.

[1*S*,9*S*(2*S*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412c) was synthesized via methods used to prepare **550q** using **513b-1** to afford **412c**.

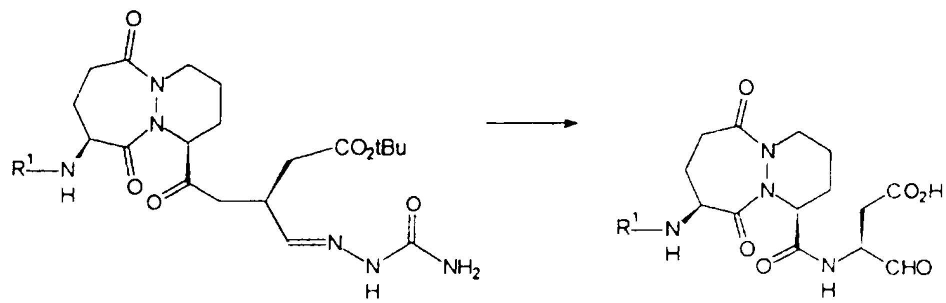
[1*S*,9*S*(2*R*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (412d) was synthesized via methods used to prepare **550q** using **513b-2** to afford **412d**: ^{1}H NMR ($CDCl_3$) δ 9.5 (1H, d), 8.9 (1H, d), 8.5 (1H, d), 7.9-7.8 (2H, m), 7.8-7.65 (2H, m), 6.55 (1H, d), 5.55 (1H, d), 5.25-5.1 (2H, m), 4.75-4.65 (1H, m), 4.65-4.6 (1H, m), 4.4-4.3 (1H, m), 3.25-3.15 (1H, m), 3.15-3.05 (1H, m), 2.95-2.8 (2H, m), 2.55-2.4 (2H, m), 2.15-1.5 (14H, m).

[1*S*,9*S*(2*S*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (412e) was synthesized via methods used to prepare **550q** using **513f-1** to afford **412e**.

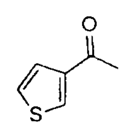
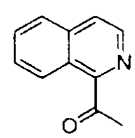
[1*S*,9*S*(2*R*,3*S*)] N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-

carboxamide, (412f) was synthesized via methods used to prepare **550q** using **513f-2** to afford **412f**.

Compounds **410** and **412** were prepared via methods used to prepare **605** from **604**.



502y, 502z **410, 412**

compound	R^1
502y, 410	
502z, 412	

[3*S*(1*S*,9*S*)] 3-[(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-9-(thiophene-3-yl-carbonylamino)-1-carboxamido]-4-oxobutanoic acid (410), was purified by flash chromatography (5-25% methanol in dichloromethane) to give 296mg (94%) of a colourless solid: mp. 90-200°C; IR (KBr) 3338, 3096, 2950, 1787, 1726, 1657, 1546, 1420, 1279, 1258, 1125, 1092, 984,

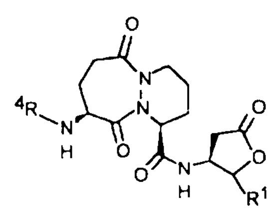
933; ^{1}H NMR (CD_3OD) δ 8.41 (1H, d), 8.13 (1H, d), 7.54-7.41 (3H, m), 7.20 (1H, d), 5.19-5.11 (1H, m), 4.54-4.30 (1H, m), 3.27 (1H, m), 3.18-3.03 (1H, m), 2.81-2.64 (2H, m), 2.56-1.59 (7H, m). Anal. Calcd for $C_{19}H_{22}N_4O_7S \cdot 2.5H_2O$: C, 46.05; H, 5.49; N, 11.31. Found: C, 46.36; H, 5.25; N, 11.10. MS (ES^+) 449 (M - 1, 80%), 113 (100). Accurate mass calculated for $C_{19}H_{23}N_4O_7S$ (MH^+): 451.1287. Found: 451.1295.

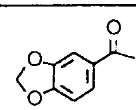
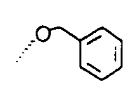
[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoic acid (412) was prepared by a similar method to that described for compound **605** to afford a white glassy solid (69%): mp. 138-141°C; $[\alpha]_D^{23}$ -105.5° (c 0.5, CH_2Cl_2); IR (KBr) 3375, 1787, 1659, 1515, 1421, 1278, 1256; ^{1}H NMR ($CDCl_3$) δ 9.32 (1H, m), 8.79 (1H, m), 8.47 (1H, m), 7.86-7.64 (4H, m), 5.31, 5.18, 4.59, 4.37 (4 or 5H, m), 3.55-2.76, 2.49-2.39, 2.05, 1.65 (11H, 4m). Anal. Calcd for $C_{24}H_{25}N_5O_7 \cdot 1.5H_2O$: C, 55.17; H, 5.40; N, 13.40. Found: C, 54.87; H, 5.22; N, 13.15. MS (ES^+, m/z) 494 (M^+ - 1, 100%).

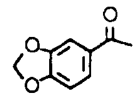
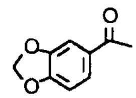
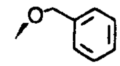
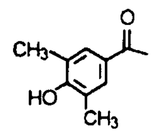
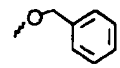
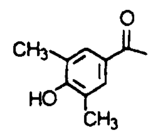
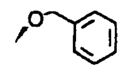
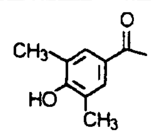
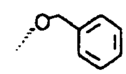
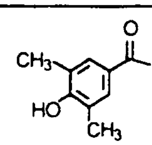
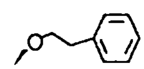
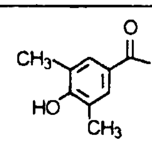
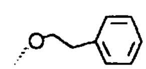
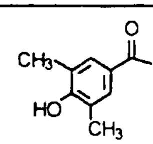
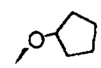
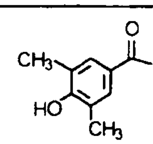
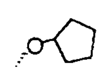
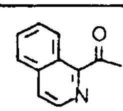
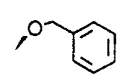
[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo—1,2,3,4,7,8,9,10-octahydro-9-(thiophene-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-carbonylamino)-1-carboxamido]-4-oxobutanoate semicarbazone (502y), was synthesized via methods used to prepare **604** from **603** to afford a pale cream powder: mp. 120-180°C; $[\alpha]_D^{23}$ -109° (c 0.18, CH_2Cl_2); IR (KBr) 3478, 3327, 1670, 1582, 1543, 1421, 1279, 1257, 1155; ^{1}H NMR ($CDCl_3$, CD_3OD) δ 8.04 (1H, m), 7.49 (1H, m), 7.38 (1H, m), 7.17 (1H, m),

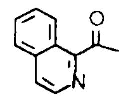
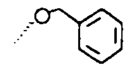
5.17-5.01 (2H, m), 4.86 (1H, m), 4.61-4.50 (1H, m), 3.45-3.29 (2H, m), 3.21-3.03 (1H, m), 2.79-2.54 (3H, m), 2.43-2.33 (1H, m), 2.11-1.66 (5H, m), 1.44 (9H, s). Anal. Calcd for $C_{24}H_{33}N_7O_7S{\cdot}H_2O$: C, 49.56; H, 6.07; N, 16.86; S, 5.51. Found: C, 49.51; H, 5.93; N, 16.31; S, 5.17. MS (ES^+) 586 (100%), 564 (M^+ + 1, 1.59). Accurate mass calculated for $C_{24}H_{34}N_7O_7S$ (MH^+): 564.2240. Found: 564.2267.

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoate semicarbazone (502z), was prepared by a similar method to that described for compound **604** to afford a pale yellow solid (90%): mp. 142-145°C; $[\alpha]_D^{24}$ -136.5° (c 0.06, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 9.51-9.46 (1H, m), 9.11 (1H, s), 8.83 (1H, d, J = 7.8), 8.53 (1H, d, J = 5.5), 7.89-7.83 (2H, m), 7.77-7.65 (2H, m), 7.55 (1H, d, J = 7.2), 7.18 (1H, d, J = 2.7), 5.26-5.12 (2H, m), 4.87 (1H, m), 4.59 (1H, m), 3.25-3.12 (2H, m), 2.95-2.76 (2H, m), 2.59-2.38, 2.18-1.94, 1.70 (5H, 3m), 1.44 (9H, s).



compound	R^4	R^1
415a		

compound	R^4	R^1
415b		
415c		
214w-1		
214w-2		
214w-3		
214w-4		
214w-5		
214w-6		
214w-7		
412g		

compound	R^4	R^1
412h		

[1*S*,9*S*(2*S*,3*S*)] **N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (415a)** was synthesized via methods used to prepare **550q** to afford **415a**.

[1*S*,9*S*(2*RS*,3*S*)] **N-(2-Ethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxy benzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (415b)** was synthesized via methods used to prepare **550q** to afford **415b**.

[1*S*,9*S*(2*R*,3*S*)] **N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(methylenedioxy benzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, (415c)** was synthesized via methods used to prepare **550q** to afford **415c**.

[1*S*,9*S*(2*RS*,3*S*)] **N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, (214w-1)** was synthesized via methods used to prepare **550q** to afford **214w-1**.

[1*S*,9*S*(2*R*,3*S*)] **N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-**

1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, **(214w-2)** was synthesized via methods used to prepare **550q** to afford **214w-2**.

[1*S*,9*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, **(214w-3)** was synthesized via methods used to prepare **550q** to afford **214w-3**.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, **(214w-4)** was synthesized via methods used to prepare **550q** to afford **214w-4**.

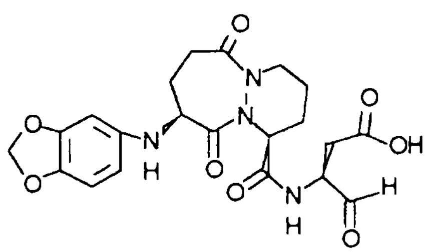
[1*S*,9*S*(2*S*,3*S*)] N-(2-Phenethoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, **(214w-5)** was synthesized via methods used to prepare **550q** to afford **214w-5**.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, **(214w-6)** was synthesized via methods used to prepare **550q** to afford **214w-6**.

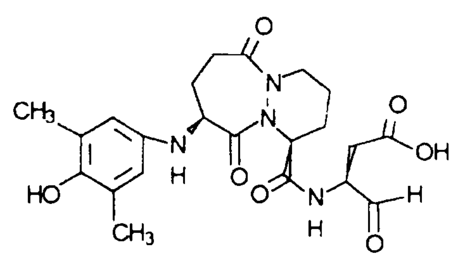
[1*S*,9*S*(2*S*,3*S*)] N-(2-Cyclopentoxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(3,5-dimethyl-4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide, **(214w-7)** was synthesized via methods used to prepare **550q** to afford **214w-7**.

[1*S*,9*S*(2*R*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, **(412g)** was synthesized via methods used to prepare **550q** to afford **412g**.

[1*S*,9*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-9-(isoquinolin-1-oylamino)-1,2,3,4,7,8,9,10-octahydro-6-H-pyridazino[1,2-a][1,2] diazepine-1-carboxamide, **(412h)** was synthesized via methods used to prepare **550q** to afford **412h**.



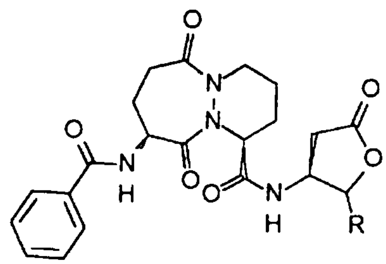
415



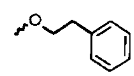
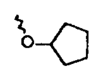
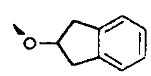
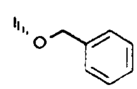
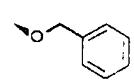
214w

[3*S*(1*S*,9*S*)]3-(9-(4,5-Methylenedioxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid **(415)**, was synthesized by the method used to prepare **2002** from **2001** to afford **415**.

[3*S*(1*S*,9*S*)]3-(9-(3,5-Dichloro-4-hydroxybenzoyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (214w), was synthesized by the method used to prepare **2002** from **2001** to afford **214w**.



2100k-o

compound	R
2100k	
2100l	
2100m	
2100n	
2100o	

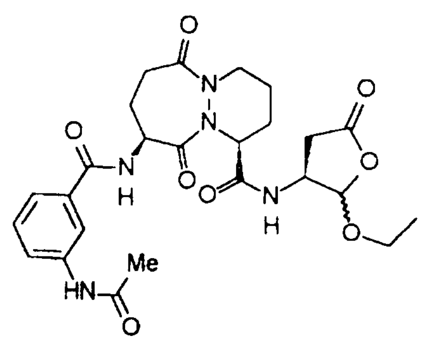
[1*S*,9*S*(2*RS*,3*S*)] 9-Benzoylamino-6,10-dioxo—1,2,3,4,7,8,9,10-octahydro-N-(2-phenethyloxy-5-oxotetrahydrofuran-3-yl)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100k), was prepared by a similar method as compound **213e** to afford a mixture of diastereoisomers (75/25) as a white solid (258mg, 83%): mp. 101°C; $[\alpha]_D^{25}$ -96° (c 0.2, CH_2Cl_2); IR (KBr) 3328, 2935, 2978, 1732, 1669, 1603, 1483, 1450, 1414, 1237, 1155, 1082, 989, 755; ^{1}H NMR ($CDCl_3$) δ 7.84-7.80 (2H, m), 7.54-7.17 (8H, m), 7.06-6.99 (1H, m), 6.25 (1H, d, J = 7.9H), 5.41 (0.75H, d, J = 5.4H), 5.31 (0.25H, bs), 5.23-5.09 (1H, m), 4.93-4.87 (1H, m), 4.68-4.51 (2H, m), 4.40-4.33 (0.25H, m), 4.24-4.14 (0.75H, m), 3.95-3.70 (1H, m), 3.30-3.13 (1H, m), 3.14-2.78 (5H, m), 2.47-2.21 (2H, m), 2.05-1.50 (5H, m). Anal. Calcd for $C_{29}H_{32}N_4O_7 \cdot 0.5H_2O$: C, 62.47; H, 5.97; N, 10.05. Found: C, 62.17; H, 5.83; N, 9.97. MS (ES^+) 549.

[1*S*,9*S*(2*RS*,3*S*)] 9-Benzamido-N-(2-cyclopentyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo—1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100l), was prepared by a similar method as **213e**, (74%) as a colourless solid: mp. 172-80°C; $[\alpha]_D^{23}$ -91.5° (c 0.1, CH_2Cl_2); IR (KBr) 3290, 1792, 1677, 1657, 1642, 1544, 1425, 1280, 1259, 1124, 977; ^{1}H NMR ($CDCl_3$) δ 7.80 (2H, m), 7.46 (3.5H, m), 7.00 (1H, d, J = 6.7), 6.48 (0.5H, d, J = 7.9), 5.55 (0.5H, d, J = 5.3), 5.19 (2H, s + m), 4.93 (0.5H, m), 4.62 (1.5H, m), 4.34 (1H, m), 4.18 (0.5H, m), 3.28-2.70 (4H, m), 2.49-2.29 (2H, m), 205-1.48 (15H, m).

[1*S*,9*S*(2*R*,3*S*)] 9-Benzamido-6,10-dioxo-N-[2-(2-indanyloxy)-5-oxo-tetrahydrofuran-3-yl]-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100m), was prepared by a similar method as **213e**, (76%) as a colourless solid: mp. ~140°C, remelts 187-9°C; $[\alpha]_D^{23}$ -96.9° (c 0.11, CH_2Cl_2); IR (KBr) 3507, 3308, 3251, 1772, 1660, 1641, 1566, 1545, 1457, 1424, 1346, 1326, 1302, 1275, 1258, 1136, 1085, 1018, 981; ^1H NMR ($CDCl_3$) δ 7.78 (2H, m), 7.53 (3H, m), 7.19 (4H, m), 6.91 (1H, d, J = 7.4), 6.27 (1H, d, J = 7.6), 5.66 (1H, d, J = 5.3), 5.10 (1H, m), 4.96 (1H, m), 4.75 (2H, m), 4.52 (1H, m), 3.08 (3H, m), 3.03-2.71 (5H, m), 2.48-2.31 (2H, m), 1.90-1.40 (4H, m), 1.22 (1H, m).

[1*S*,9*S*(2*S*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100n), was prepared by a similar method to that described for compound **213e** to afford a white glassy solid (76%): mp. 112-5°C; $[\alpha]_D^{23}$ -62.0° (c 0.1, CH_2Cl_2); IR (KBr) 3305, 1789, 1677, 1665, 1535, 1422, 1279, 1256, 1119, 942, 700; ^1H NMR ($CDCl_3$) δ 7.84 (2H, m), 7.58-7.27 (9H, m), 6.99 (1H, d, J = 7.8), 5.23 (1H, s), 5.23-5.11 (1H, m), 4.89 (1H, m), 4.76 (1H, d, J = 11.3), 4.55 (1H, d, J = 11.4), 4.58-4.43 (2H, m), 3.30-2.96, 2.81-2.69, 2.46-2.37, 2.16-1.66 (10H, 4m), 2.27 (1H, d, J = 17.8). Anal. Calcd for $C_{28}H_{30}N_4O_7 \cdot 0.5H_2O$: C, 61.87; H, 5.75; N, 10.32. Found: C, 61.88; H, 5.70; N, 10.33. MS (ES^+, m/z) 535 (M^+ + 1, 100%).

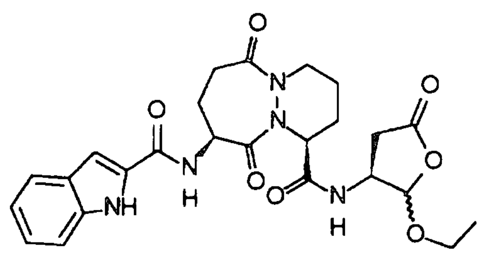
[1*S*,9*S*(2*R*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (2100o), (containing about 7% of (2*S*)), was prepared by a similar method to that described for compound **213e** to afford a white glassy solid (81%): mp. 115-7°C; $[\alpha]_D^{23}$ -121.8° (c 0.11, CH_2Cl_2); IR (KBr) 3326, 1792, 1659, 1535, 1421, 1278, 1257, 1124, 978; ^1H NMR ($CDCl_3$) δ 7.82 (2H, m), 7.58-7.24 (8H, m), 6.90 (1H, d, J = 7.3), 6.49 (1H, d, J = 7.7), 5.57 (1H, d, J = 5.5), 5.11 (2H, m), 4.91 (1H, d, J = 11.4), 4.57 (1H, d, J = 11.1), 4.81-4.68 (1H, m), 4.65-4.54 (1H, m), 3.18-2.71 2.52-2.30, 2.05-1.62 (11H, 3m). Anal. Calcd for $C_{28}H_{30}N_4O_7 \cdot 0.5H_2O$: C, 61.87; H, 5.75; N, 10.32. Found: C, 61.70; H, 5.71; N, 10.15. MS (ES^+, m/z) 535 (M^+ + 1, 94.3%), 557 (100%).



550n

[1*S*,9*S*(2*RS*,3*S*)] 9-(3-Acetamido)benzoylamino-6,10-dioxo-N-(2-ethoxy-5-oxo-tetrahydrofuran-3-yl)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550n), was prepared by a similar method as compound **213e** to

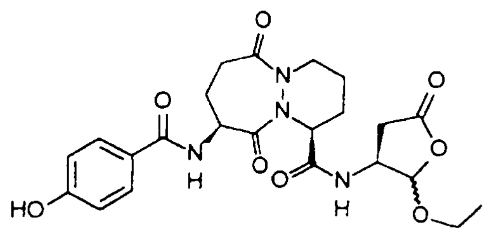
afford a mixture of diastereoisomers (65/35) as a tan powder (390mg, 28%): mp. 139-145°C; $[\alpha]_D^{23}$ -104° (c 0.2, MeOH); IR (KBr) 3318, 2405, 2369, 1792, 1660, 1591, 1549, 1484, 1422, 1257, 1117; ^{1}H NMR (D_6-DMSO) δ 10.1 (1H, s), 8.80 (0.65H, d, J = 6.6), 8.58 (0.35H, d, J = 6.6), 8.59 (1H, d, J = 7.0), 8.06 (1H, bs), 7.83-7.79 (1H, m), 7.61-7.57 (1H, m), 7.47-7.39 (1H, m), 5.61 (0.35H, d, J = 5.0), 5.37 (0.65H, bs), 5.17-5.14 (0.35H, m), 5.08-5.06 (0.65H, m), 4.92-4.86 (1H, m), 4.67-4.61 (0.35H, m), 4.47-4.41 (0.65H, m), 4.28-4.11 (1H, 2m), 3.80-3.59 (2H, m), 3.23-2.75 (3H, m), 2.61-1.48 (7H, m), 2.10 (3H, s), 1.25 and 1.17 (3H, 2t, J = 5.8). MS (ES^+) 528.



550o

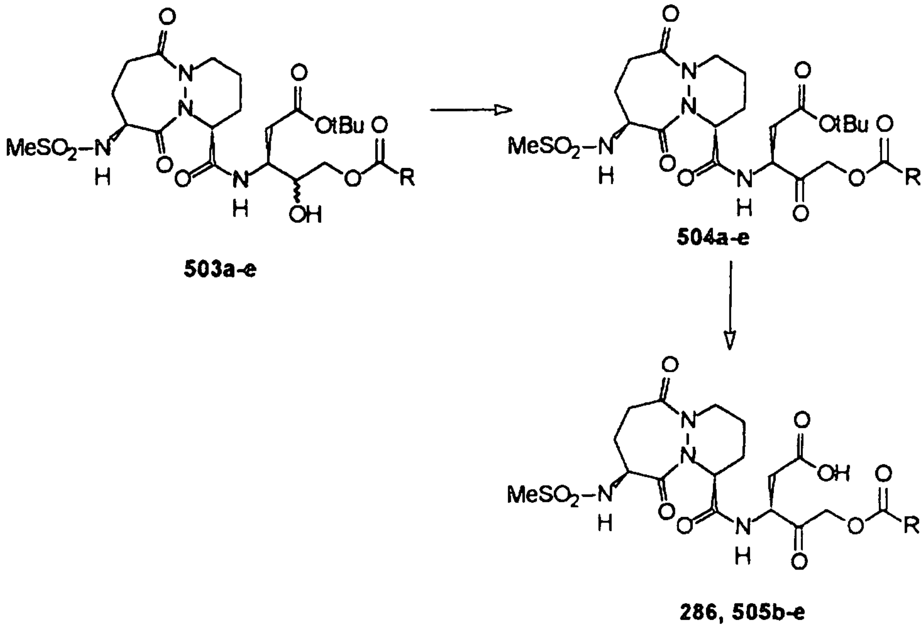
[1*S*,9*S*(2*RS*,3*S*)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-9-(2-indoloylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550o), was synthesized by a similar method as compound **213e** to afford a colourless solid (1.071g, 80%): mp. 155-70°C; $[\alpha]_D^{22}$ -75.8° (c 0.26, CH_2Cl_2); IR (KBr) 3314, 2941, 1791, 1658, 1545, 1420, 1341, 1312, 1252, 1181, 1118, 939, 749; ^{1}H NMR ($CDCl_3$) δ 9.45 (0.5H, s), 9.34 (0.5H, s), 7.68-7.62 (1H, m), 7.49-7.39 (2H, m), 7.33-7.26

(1H, m), 7.18-7.03 (3H, m), 5.49 (0.5H, d), 5.30 (0.5 H, s), 5.26-5.13 (1H, m), 4.90-4.83 (0.5H, m), 4.76-4.49 (1H, m), 4.42-4.35 (0.5H, m), 3.97-3.74 (1H, m), 3.72-3.53 (1H, m), 3.35-2.64 (4H, m), 2.50-2.37 (1H, m), 2.20-1.82 (5H, m), 1.69-1.50 (2H, m), 1.30-1.19 (3H, m).



550p

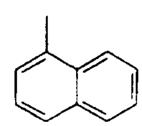
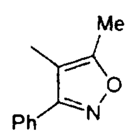
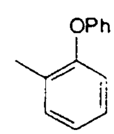
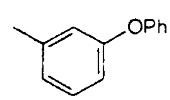
[1*S*,9*S*(2*RS*,3*S*)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-9-(4-hydroxybenzoyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (550p), was prepared by a similar method as compound **213e** to afford a mixture of diastereoisomers as a white foam (820mg, 47%): $[\alpha]_D^{24}$ -75° (c 0.16, CH_2Cl_2); IR (KBr) 3401, 2937, 1791, 1657, 1609, 1539, 1505, 1423, 1277, 1177, 1118; ^1H NMR ($CDCl_3$) δ 8.07-8.05 (1H, m), 7.67 (2H, d, J = 7.9), 7.38-7.29 (2H, m), 6.80 (2H, d, J = 8.5), 5.49 (0.5H, d, J = 4.6), 5.23 (0.5H, bs), 5.24-5.20 (1H, m), 5.12-5.08 (1H, m), 4.68-4.29 (2H, m), 3.92-3.45 (3H, m), 3.32-2.30 (2H, m), 2.80-1.56 (11H, m), 1.21 (3H, t, J = 7.0H).

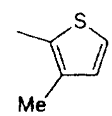


503a-e

504a-e

286, 505b-e

compound	R
503a 504a 286	
503b 504b 505b	
503c 504c 505c	
503d 504d 505d	

503e 504e 505e	

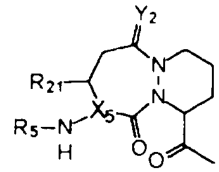
[3*S*,4*R*(1*S*,9*S*)] t-Butyl 3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxy-5-(1-naphthoyloxy)pentanoate (503a), was prepared from **212b** and (3*S*,4*R*) t-butyl (N-allyloxycarbonyl)-3-amino-4-hydroxy-5-(1-naphthoyloxy)pentanoate by the method described for **(213e)** to afford 533mg (81%) of an off-white foam: $[\alpha]_D^{22}$ -81.4° (c 0.5, CH_2Cl_2); IR(KBr) 3342, 2976, 1719, 1664, 1328, 1278, 1246, 1153, 1137. ^1H NMR ($CDCl_3$) δ 8.86 (1H, d, J = 8.4), 8.21 (1H, dd, J = 1.3, 7.3), 8.03 (1H, d, J = 8.1), 7.88 (1H, d, J = 8.6), 7.66-7.45 (3H, m), 7.23 (1H, d, J = 8.6), 5.96 (1H, d, J = 9.2), 5.30 (1H, m), 4.59-4.33 (5H, m), 4.24 (1H, m), 3.96 (1H, brd), 3.29 (1H, m), 2.95 (1H, m), 2.93 (3H, s), 2.69-2.50 (3H, m), 2.36 (1H, m), 1.96 (4H, m), 1.62 (1H, m), 1.41 (9H, s). Anal. Calcd for $C_{31}H_{40}N_4O_{10}S \cdot 0.25H_2O$: C, 55.97; H, 6.14; N, 8.42. Found: C, 55.90; H, 6.11; N, 8.23. M.S. (ES^+) 683 (M+Na, 100%), 661 (M+1,39), 605 (78).

[3*S*(1*S*,9*S*)] t-Butyl 3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(1-naphthoyloxy)-4-oxopentanoate (504a), was synthesized from **503a** via method used to prepare **216e** from **215e** to afford 446mg (91%) of a colourless foam: $[\alpha]_D^{21}$ -111.6°

(c 0.5, CH_2Cl_2); IR (KBr) 3319, 2978, 2936, 1723, 1670, 1413, 1370, 1329, 1278, 1246, 1153. ^1H NMR ($CDCl_3$) δ 8.87 (1H, d, J = 8.9), 8.29 (1H, d, J = 7.2), 8.06 (1H, d, J = 8.3), 7.90 (1H, d, J = 8.2), 7.66-7.48 (3H, m), 7.37 (1H, d, J = 8.1), 5.61 (1H, d, J = 9.0), 5.31 (1H, m), 5.22 (1H, AB, J = 16.9), 5.09 (1H, AB, J = 16.92), 4.99 (1H, m), 4.65-4.43 (2H, m), 3.28 (1H, m), 2.96 (3H, s), 2.86 (2H, m), 2.59 (1H, m) 2.38 (1H, dd, J = 6.8, 13.2), 2.21-1.70 (6H, m), 1.45 (9H, s). Anal. Calcd for $C_{31}H_{38}N_4O_{10}S \cdot 0.25H_2O$. C, 56.14; H, 5.85; N, 8.45. Found: C, 56.11; H, 5.83; N, 8.29. M.S. (ES^+) 657 (M-1, 100%).

[3*S*(1*S*,9*S*)] 3-(6,10-Dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(1-naphthoyloxy)-4-oxopentanoic acid (286), was prepared from **504a** by the method described for **217** to afford 356mg (93%) of a white powder: mp 120-123°C; $[\alpha]_D^{23}$ -121° (c 0.194, CH_2Cl_2); IR (KBr) 3314, 2937, 1722, 1663, 1412, 1328, 1278, 1245, 1195, 1132. ^1H NMR (d6-DMSO) δ 12.63 (1H, brs), 8.94 (1H, d, J = 7.4), 8.78 (1H, d, J = 8.6), 8.26 (2H, m), 8.11 (1H, d, J = 8.0), 7.77-7.62 (4H, m), 5.28 (2H, s), 5.21 (1H, m), 4.82 (1H, m), 4.44-4.29 (2H, m), 3.31 (1H, m), 2.98 (3H, s), 2.98-2.86 (2H, m), 2.72 (1H, dd, J = 7.3, 16.9), 2.40 (1H, m), 2.24-1.84 (4H, m), 1.69 (2H, m). Anal. Calcd for $C_{27}H_{30}N_4O_{10}S \cdot H_2O$: C, 52.25; H, 5.20; N, 9.03. Found: C, 52.11; H, 4.97; N, 8.89. M.S. (ES^+) 601 (M-1, 100%).

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-9-

(e10)  ;

R_3 is $-CO-CH_2-T_1-R_{11}$ and R_{11} is $-Ar_4$;

R_5 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$, and
$-C(O)-NH-R_{10}$;

X_5 is CH;

Y_2 is O;

T_1 is O or S;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl,

pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

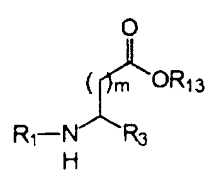
each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

35. A compound represented by the formula:

(II) 

wherein:

m is 1;

R_1 is:

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 O
/ \
   CH2;
\ /
 O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

34. The compound according to claims 32 or 33, wherein:

m is 1;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl,

$-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

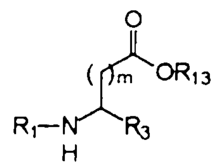
R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

OR_{13} is optionally -N(H)-OH;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

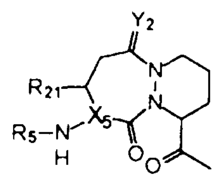
each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

(II) 

wherein:

m is 1 or 2;

R_1 is:

(e10)  ;

R_3 is -C(O)-H;

R_5 is selected from the group consisting of:
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$;

X_5 is CH;

Y_2 is H_2 or O;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a

and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

```
 O
/ \
   CH2;
\ /
 O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

33. A compound represented by the formula:

Y_2 is H_2 or O;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

OR_{13} is optionally -N(H)-OH;

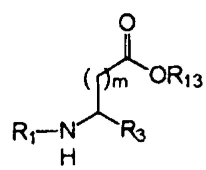
each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,

with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

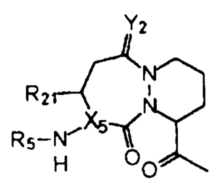
32. A compound represented by the formula:

(II) 

wherein:

m is 1 or 2;

R_1 is:

(e10)  ;

R_3 is $-C(O)-CH_2-T_1-R_{11}$; T_1 is O; and R_{11} is $-C(O)-Ar_4$;

R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$;

X_5 is CH;

wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
   O
  / \
     CH2,
  \ /
   O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

30. The compound according to claims 26 or 27, wherein R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-C(O)-R_{10}$,
$-R_9$, and
$-C(O)-C(O)-OR_{10}$.

31. The compound according to claim 30, wherein:

m is 1;

T_1 is O or S;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl,

T_1 is O or S;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of -NH_2, -CO_2H, -Cl, -F, -Br, -I, -NO_2, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, -R_5, -OR_5, -NHR_5, -OR_9, -NHR_9, -R_9, -C(O)-R_{10}, and

```
  O
 / \
    CH2;
 \ /
  O
```

provided that when -Ar_3 is substituted with a Q_1 group which comprises one or more additional -Ar_3 groups, said additional -Ar_3 groups are not substituted with another -Ar_3.

28. The compound according to claims 26 or 27, wherein R_5 is selected from the group consisting of:

-C(O)-R_{10},
-C(O)O-R_9, and
-C(O)-NH-R_{10}.

29. The compound according to claim 28, wherein:

m is 1;

consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

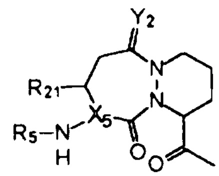
R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

OR_{13} is optionally -N(H)-OH;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said

(e10)  ;

R_3 is $-C(O)-CH_2-T_1-R_{11}$ and R_{11} is $-(CH_2)_{1-3}-Ar_4$;

R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$$-C(O)-N\begin{matrix} / R_{10} \\ \backslash R_{10} \end{matrix},$$

$-S(O)_2-R_9$,

$-C(O)-CH_2-O-R_9$,

$-C(O)C(O)-R_{10}$,

$-R_9$,

$-H$, and

$-C(O)C(O)-OR_{10}$,

X_5 is CH;

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group

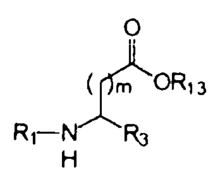
containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, $-Cl$, $-F$, $-Br$, $-I$, $-NO_2$, $-CN$, $=O$, $-OH$, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

```
  O
 / \
    CH2;
 \ /
  O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

27. A compound represented by the formula:

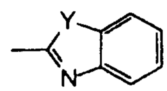
(II) 

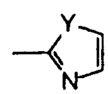
wherein:

m is 1 or 2;

R_1 is:

group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally

$-S(O)_2-R_9$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
-H, and
$-C(O)C(O)-OR_{10}$,

X_5 is CH;

Y_2 is H_2 or O;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

OR_{13} is optionally -N(H)-OH;

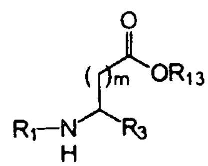
each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

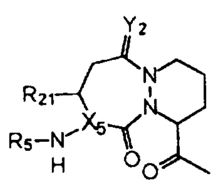
26. A compound represented by the formula:

(II) 

wherein:

m is 1 or 2;

R_1 is:

(e10)  ;

R_3 is $-CO-Ar_2$;

R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$$-C(O)-N\begin{matrix} / R_{10} \\ \backslash R_{10} \end{matrix},$$

wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
   O
  / \
     CH2,
  \ /
   O
```

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

24. The compound according to any one of claims 19-21, wherein R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

25. The compound according to claim 24, wherein:

m is 1;

T_1 is O or S,

provided that when R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, $-OH$, $-OR_9$, $-CO_2H$,

provided that when R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

Ar_2 is (hh);

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

16. The compound according to claim 8, wherein R_1 is (e10) and X_5 is N.

17. The compound according to claim 16, wherein R_3 is CO-Ar_2.

18. The compound according to claim 16, wherein R_3 is -C(O)-CH_2-T_1-R_{11} and R_{11} is -$(CH_2)_{1-3}$-Ar_4.

19. The compound according to claim 16, wherein:

R_3 is -C(O)-CH_2-T_1-R_{11};

T_1 is O; and

R_{11} is -C(O)-Ar_4.

20. The compound according to claim 16, wherein R_3 is -C(O)-H.

21. The compound according to claim 16, wherein R_3 is -CO-CH_2-T_1-R_{11} and R_{11} is -Ar_4.

22. The compound according to any one of claims 19-21, wherein R_5 is selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9, and

-C(O)-NH-R_{10}.

23. The compound according to claim 22, wherein:

m is 1;

T_1 is O or S,

Y is O;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

m is 1;

ring C is benzo, pyrido, or thieno;

R_3 is selected from the group consisting of -C(O)-H, -C(O)-Ar_2, and -C(O)CH_2-T_1-R_{11};

R_5 is selected from the group consisting of:

-C(O)-R_{10}, wherein R_{10} is -Ar_3;

-C(O)O-R_9, wherein R_9 is -CH_2-Ar_3;

-C(O)C(O)-R_{10}, wherein R_{10} is -Ar_3;

-R_9, wherein R_9 is a C_{1-2} alkyl group substituted with -Ar_3; and

-C(O)C(O)-OR_{10}, wherein R_{10} is -CH_2Ar_3;

T_1 is O or S;

R_6 is H;

R_8 is selected from the group consisting -C(O)-R_{10}, -C(O)-CH_2-OR_{10}, and -C(O)CH_2-N(R_{10})(R_{10}), wherein R_{10} is H, CH_3, or -CH_2CH_3;

R_{11} is selected from the group consisting of -Ar_4, -$(CH_2)_{1-3}$-Ar_4, and -C(O)-Ar_4;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with -Ar_3, -OH, -OR_9, -CO_2H, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

Ar_2 is (hh);

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

```
     O
    / \
       CH2;
    \ /
     O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

9. The compound according to claim 8, wherein R_1 is (e11).

10. The compound according to claim 8, wherein R_1 is (e12).

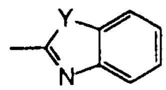
11. The compound according to claim 8, wherein R_1 is (y1).

12. The compound according to claim 8, wherein R_1 is (y2).

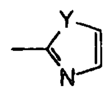
13. The compound according to claim 8, wherein and R_1 is (z).

14. The compound according to claim 8, wherein R_1 is (w2).

15. The compound according to claim 14, wherein:

(hh) 

, and

(ii) 

,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

$-Ar_4$,

$-(CH_2)_{1-3}-Ar_4$,

-H, and

$-C(O)-Ar_4$;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

OR_{13} is optionally -N(H)-OH;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

$$-C(O)-N\begin{matrix} R_{10} \\ R_{10}, \end{matrix}$$

$-S(O)_2-R_9$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$, and
$-C(O)C(O)-OR_{10}$,

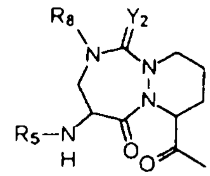
Y_2 is H_2 or O;

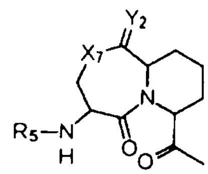
X_7 is $-N(R_8)-$ or $-O-$;

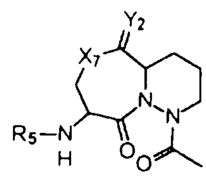
each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
$-H$, and
$-C(O)-C(O)-OR_{10}$;

(y1)  ;

(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

-C(O)-CH_2-T_1-R_{11},

-C(O)-CH_2-F,

-C=N-O-R_9, and

-CO-Ar_2;

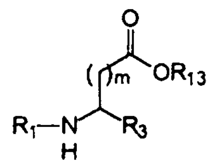
R_5 is selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

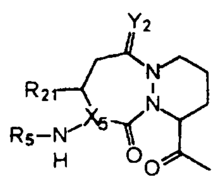
8. A compound represented by the formula:

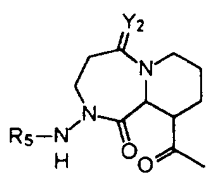
(II) 

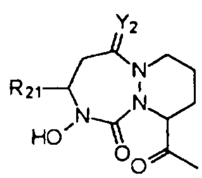
wherein:

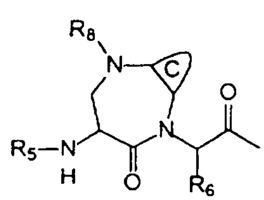
m is 1 or 2;

R_1 is selected from the group consisting of the following formulae:

(e10)  , wherein X_5 is N;

(e11)  ;

(e12)  ;

(w2)  ;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-NHR_9$, $-R_9$, $-C(O)-R_{10}$, and

```
    O
   / \
      CH2,
   \ /
    O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

5. The compound according to claim 4, wherein R_5 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$, and

$-C(O)-NH-R_{10}$.

6. The compound according to claim 4, wherein R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$.

7. The compound according to claims 5 or 6, wherein:

m is 1;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a C_{1-6} straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

$-C(O)C(O)-R_{10}$,
$-R_9$,
-H, and
$-C(O)C(O)-OR_{10}$;

X_5 is -CH- or -N-;

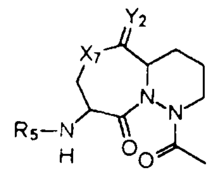
Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or -O-;

R_6 is selected from the group consisting of -H and $-CH_3$;

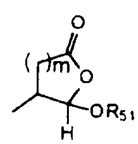
R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

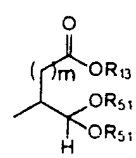
each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_2 is:

(a)  , or

(b)  ;

m is 1 or 2;

R_5 is selected from the group consisting of:

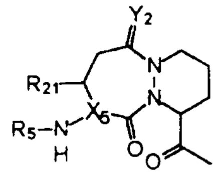
-C(O)-R_{10},

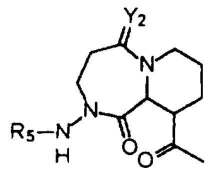
-C(O)O-R_9,

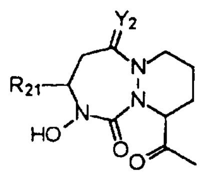
```
          R10
         /
-C(O)-N
         \
          R10,
```

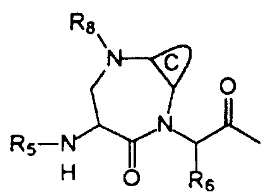
-S(O)$_2$-R_9,

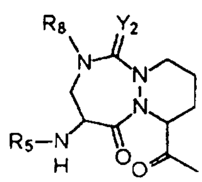
-C(O)-CH_2-O-R_9,

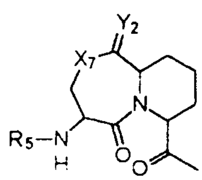
(e10)  ;

(e11)  ;

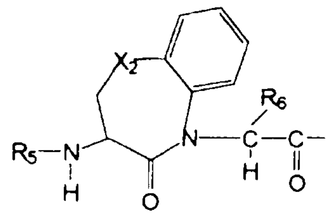
(e12)  ;

(w2)  ;

(y1)  ;

(y2)  ;

3. The compound according to claims 1 or 2, wherein the R_1 group is:

(w1)  ; wherein

X_2 is:

-O- ,

-S- ,

$-SO_2-$, or

-NH-;

optionally substituted with R_5 or Q_1 at X_2 when X_2 is -NH-; and

ring C is benzo substituted with $-C_{1-3}$ alkyl, $-O-C_{1-3}$ alkyl, -Cl, -F or $-CF_3$.

4. A compound represented by the formula:

$$(\underline{I}) \qquad \begin{array}{c} R_1-N-R_2 \\ | \\ H \end{array}$$

wherein:

R_1 is selected from the group consisting of the following formulae:

$-CO-O-R_9$,
$-SO_2-R_9$, or
$-CO-NH-R_9$,

R_7 is -H and R_6 is: -H,
$-R_9$, or
$-Ar_1$;

R_9 is a C_{1-6} straight or branched alkyl group optionally substituted with =O and optionally substituted with $-Ar_1$;

R_{10} is H or a $-C_{1-3}$ straight or branched alkyl group;

Ar_1 is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl optionally substituted with $-O-C_{1-3}$ alkyl, $-NH-C_{1-3}$ alkyl, $-N-(C_{1-3}\text{ alkyl})_2$, -Cl, -F, $-CF_3$, $-C_{1-3}$ alkyl, or

```
  O
 / \
    CH2  ;
 \ /
  O
```

Q_1 is R_9 or $-(CH_2)_{0,1,2}-T_1-(CH_2)_{0,1,2}-Ar_1$, wherein T_1 is -O- or -S-;

each X is independently selected from the group consisting of =N-, and =CH-;

each X_2 is independently selected from the group consisting of -O-, $-CH_2-$, -NH-, -S-, -SO-, and $-SO_2-$.

X_2 is O,

R_5 is benzyloxycarbonyl, and

ring C is benzo,

then R_3 cannot be $-CO-R_{13}$ when:

R_{13} is $-CH_2-O-Ar_1$ and

Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom;

or when

R_{13} is $-CH_2-O-CO-Ar_1$, wherein

Ar_1 is 2,6-dichlorophenyl.

2. The compound according to claim 1, wherein:

X_1 is -CH;

g is 0;

J is -H;

m is 0 or 1 and T is $-CO-CO_2H$, or any bioisosteric replacement for $-CO_2H$, or

m is 1 and T is $-CO_2H$;

ring C is benzo optionally substituted with $-C_{1-3}$ alkyl, $-O-C_{1-3}$ alkyl, -Cl, -F or $-CF_3$;

R_5 is:

$-CO-Ar_1$

$-SO_2-Ar_1$,

$-CO-NH_2$,

$-CO-NH-Ar_1$

$-CO-R_9$,

each Q_1 is independently selected from the group consisting of:

$-Ar_1$

$-O-Ar_1$

$-R_9$,

$-T_1-R_9$, and

$-(CH_2)_{1,2,3}-T_1-R_9$;

each Q_2 is independently selected from the group consisting of -OH, $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, $-CF_3$, and

```
  O
 / \
    CH2;
 \ /
  O
```

provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1;

each X is independently selected from the group consisting of =N-, and =CH-;

each X_2 is independently selected from the group consisting of -O-, $-CH_2-$, -NH-, -S-, -SO-, and $-SO_2-$;

each Y is independently selected from the group consisting of -O-, -S-, and -NH;

provided that when

g is 0,

J is -H,

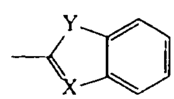
m is 1,

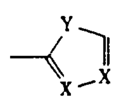
T is $-CO_2H$,

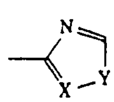
atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, $-SO_2-$, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted with $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN,

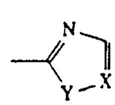
```
                                            O
                                           / \
=O, -OH, -perfluoro C1-3 alkyl,               CH2,   or -Q1;
                                           \ /
                                            O
```

each Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ and $-Q_2$:

(hh)  ;

(ii)  ;

(jj)  ; and

(kk)  ;

$$-CO-N\begin{matrix}/R_9\\ \backslash R_{10},\end{matrix}$$ and

$$-SO_2-N\begin{matrix}/R_9\\ \backslash R_{10};\end{matrix}$$

R_6 is:
-H
$-Ar_1$,
$-R_9$,
$-(CH_2)_{1,2,3}-T_1-R_9$, or
an α-amino acid side chain residue;

each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted with -OH, -F, or =O and optionally substituted with one or two Ar_1 groups;

each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

each R_{13} is independently selected from the group consisting of $-Ar_2$, $-R_4$ and $-N(OH)-R_5$;

each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring

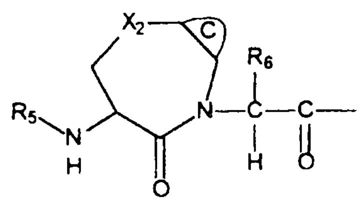
-S-,
-SO-,
$-SO_2-$,
$-NR_{10}-$,
$-NR_{10}-CO-$,
-CO-,
-O-CO-,
-CO-O-,
$-CO-NR_{10}-$,
$-O-CO-NR_{10}-$,
$-NR_{10}-CO-O-$,
$-NR_{10}-CO-NR_{10}-$,
$-SO_2-NR_{10}-$,
$-NR_{10}-SO_2-$, and
$-NR_{10}-SO_2-NR_{10}-$;

each R_5 is independently selected from the group consisting of:

-H,
$-Ar_1$,
$-CO-Ar_1$,
$-SO_2-Ar_1$,
$-CO-NH_2$,
$-SO_2-NH_2$,
$-R_9$,
$-CO-R_9$,
$-CO-O-R_9$,
$-SO_2-R_9$,

$$-CO-N\begin{matrix}/Ar_1\\ \backslash R_{10},\end{matrix}$$

$$-SO_2-N\begin{matrix}/Ar_1\\ \backslash R_{10},\end{matrix}$$

(w)  ;

wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is:
-CN,
$-CH=CH-R_9$,
$-CH=N-O-R_9$,
$-(CH_2)_{1-3}-T_1-R_9$,
$-CJ_2-R_9$,
$-CO-R_{13}$, or
$-CO-CO-N\begin{matrix}/R_5 \\ \backslash R_{10}\end{matrix}$;

each R_4 is independently selected from the group consisting of:
-H,
$-Ar_1$,
$-R_9$,
$-T_1-R_9$, and
$-(CH_2)_{1,2,3}-T_1-R_9$;

each T_1 is independently selected from the group consisting of:
CH=CH-,
-O-,

CLAIMS

We claim:

1. A compound represented by the formula:

$$\alpha \qquad \begin{array}{l} \qquad\qquad\quad (CJ_2)_m\text{-}T \\ \qquad\qquad\quad / \\ R_1\text{-}NH\text{-}X_1 \\ \qquad\qquad\quad \backslash \\ \qquad\qquad\quad (CH_2)_g\text{-}R_3 \end{array}$$

wherein:

X_1 is -CH;

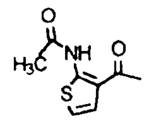
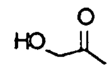
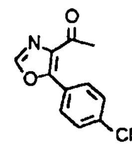
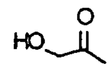
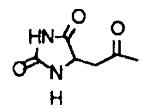
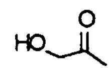
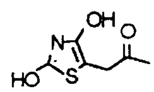
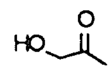
g is 0 or 1;

each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

m is 0, 1, or 2;

T is -OH, $-CO\text{-}CO_2H$, $-CO_2H$, or any bioisosteric replacement for $-CO_2H$;

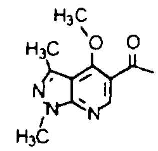
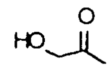
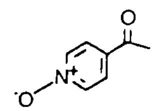
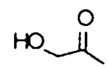
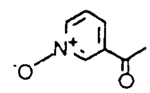
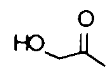
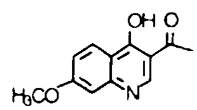
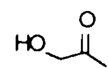
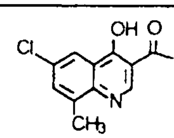
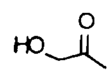
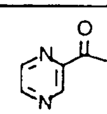
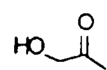
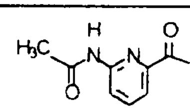
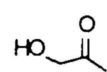
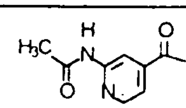
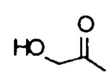
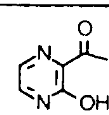
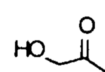
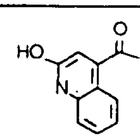
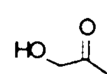
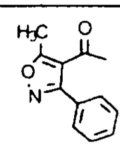
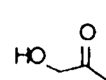
R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1, at any nitrogen by R_5, or at any atom by =O, -OH, $-CO_2H$, or halogen; and any saturated ring may optionally be unsaturated at one or two bonds;

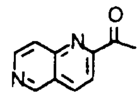
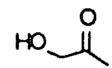
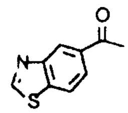
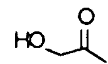
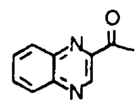
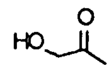
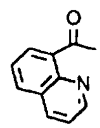
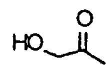
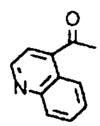
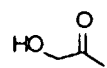
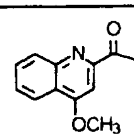
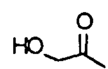
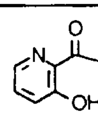
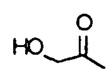
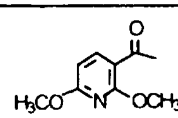
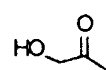
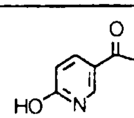
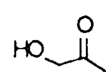
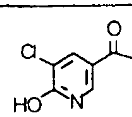
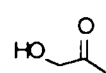
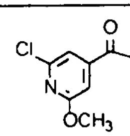
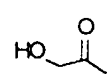
Compound	R^4	R^3
764		
765		
766		
767		

The data of the examples above demonstrate that compounds according to this invention display inhibitory activity towards IL-1ß Converting Enzyme.

Insofar as the compounds of this invention are able to inhibit ICE in vitro and furthermore, may be delivered orally to mammals, they are of evident clinical utility for the treatment of IL-1-, apoptosis-, IGIF-, and IFN-γ mediated diseases. These tests are predictive of the compounds ability to inhibit ICE in vivo.

While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments which utilize the products and processes of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific embodiments which have been presented by way of example.

Compound	R^4	R^3
753		
754		
755		
756		
757		
758		
759		
760		
761		
762		
763		

Compound	R^4	R^3
742		
743		
744		
745		
746		
747		
748		
749		
750		
751		
752		

Example 35

Compounds **736-767** were prepared by methods similar to the methods used to prepare compounds **619-635** (see, Example 13). Physical data for compounds **736-767** is listed in Table 30.

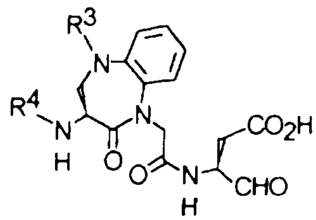
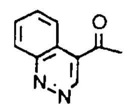
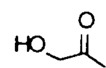
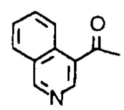
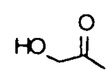
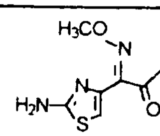
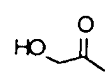
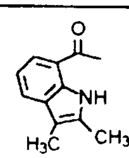
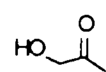
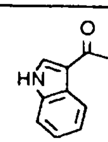
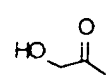
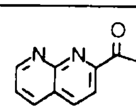
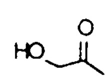
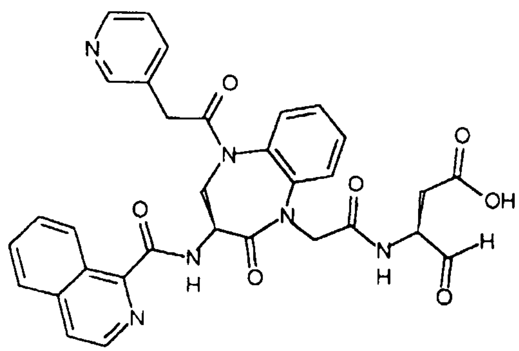
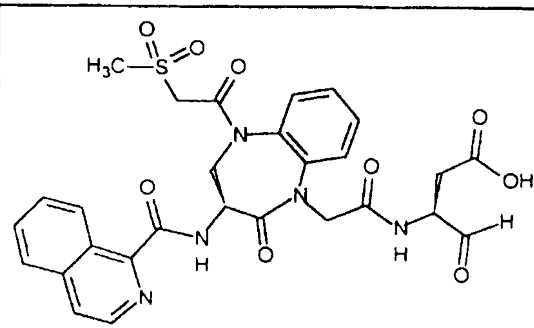
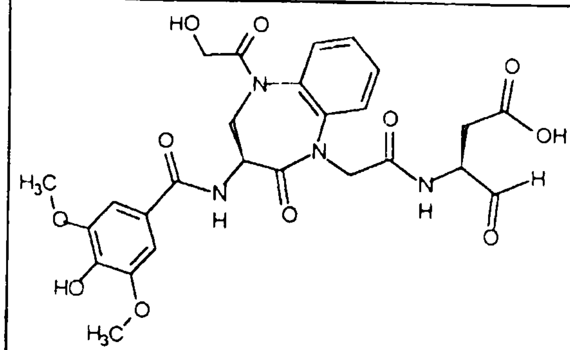
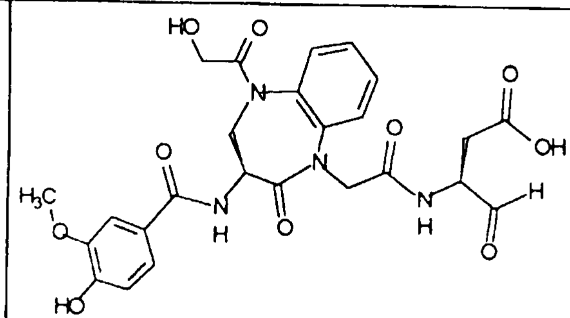
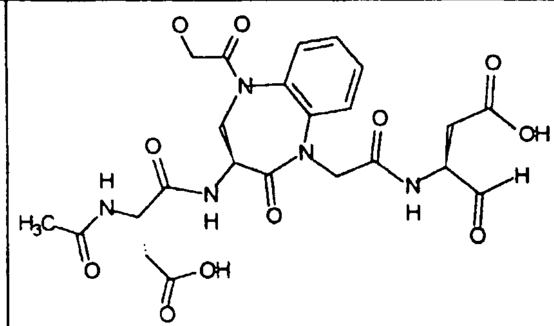
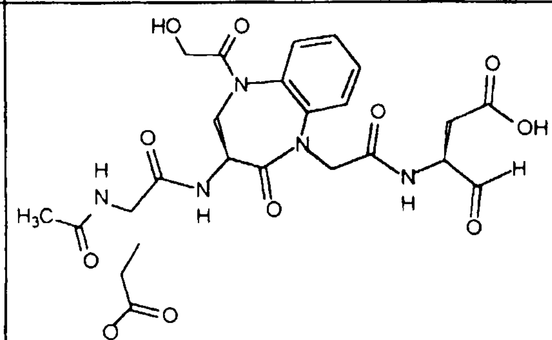


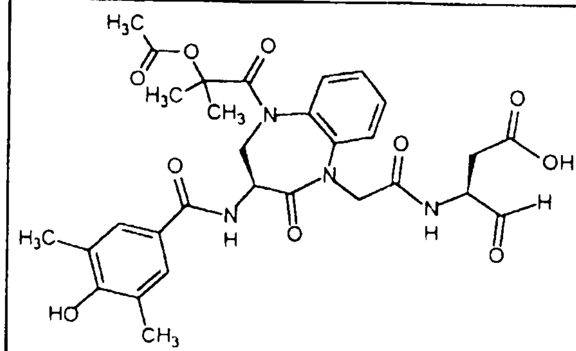
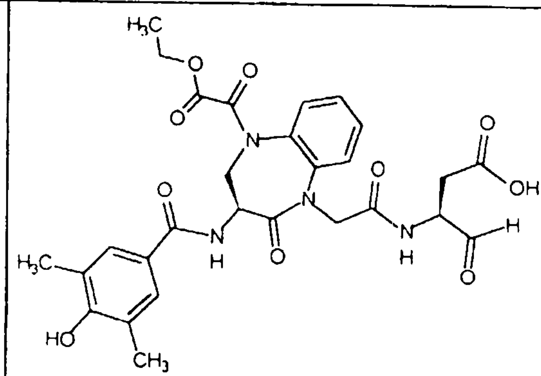
Table 30

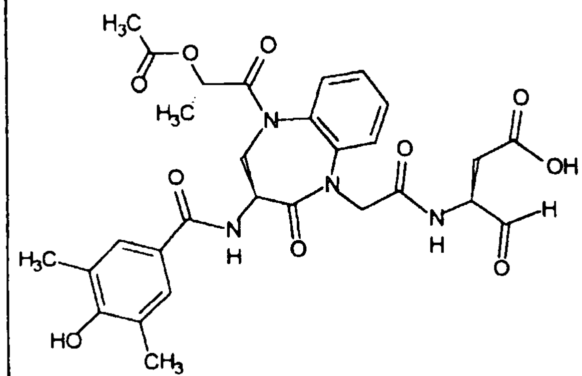
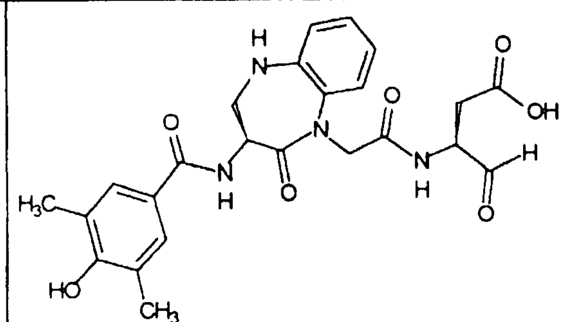
Compound	R^4	R^3
736		
737		
738		
739		
740		
741		

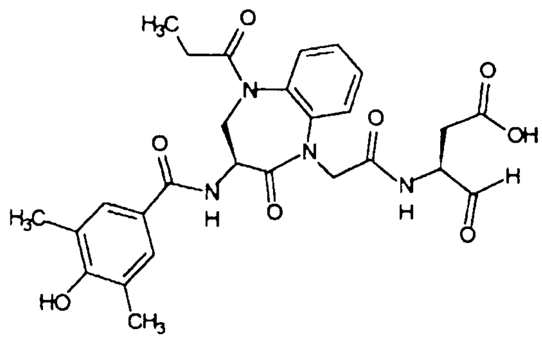
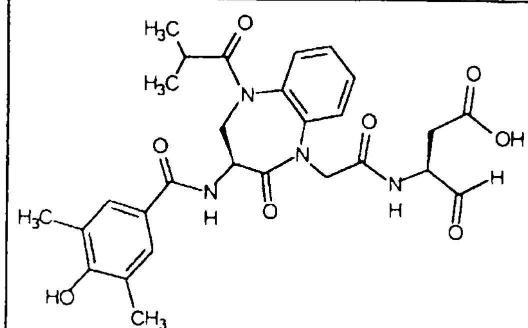
Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
734		C32H28N6O7	608.62	9.656 99%	630.6
735		C28H27N5O9S	609.62	10.887 92%	632.1

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
732		C26H28N4O11	572.53	7.640 98%	595.9
733		C25H26N4O10	542.51	7.375 98%	565.9

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
730		C23H27N5O11	549.50	3.939 96%	572.2
731		C24H29N5O11	563.53	4.298 92%	587

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
728		C30H34N4O10	610.63	11.556	634.9
729		C28H30N4O10	582.57	11.611 99%	607.3

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
726		C29H32N4O10	596.60	10.667 99%	620.8
727		C24H26N4O7	482.50	9.085 92%	506.6

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
724		C27H30N4O8	538.56	10.584 99%	563.1
725		C28H32N4O8	552.59	11.329 99%	577.2

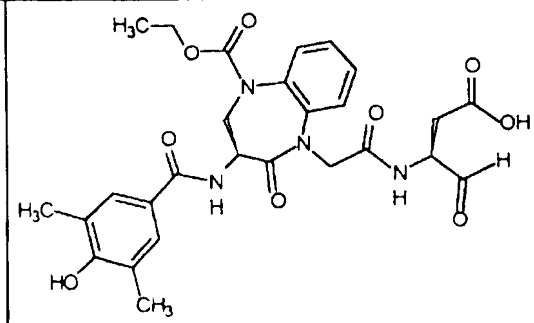
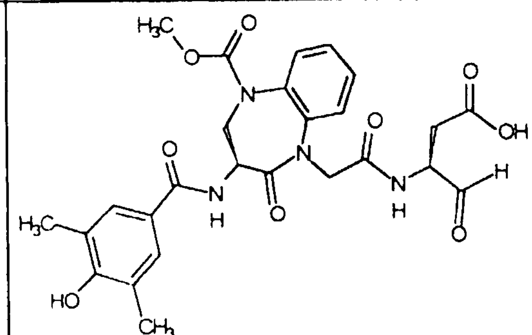
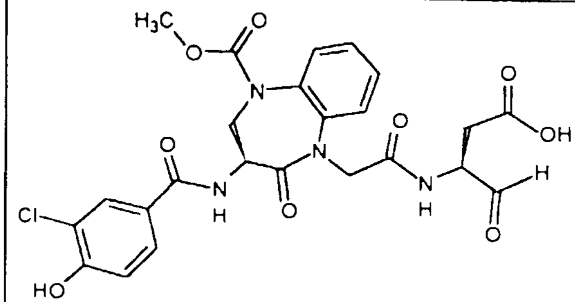
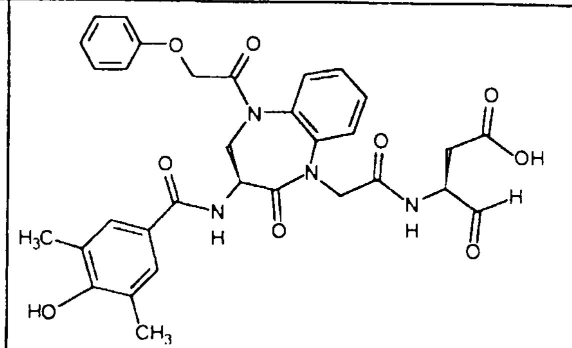
Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
722		C27H30N4O9	554.56	11.761 99%	578.2
723		C26H28N4O9	540.53	10.655 79%	564.5

Table 29

Compound	Structure	MF	MW	HPLC RT min Purity	MS (M+Na)+
720		C24H23ClN4O9	546.93	10.729 99%	568.8
721		C32H32N4O9	616.63	13.241 99%	640.4

Example 34

Compounds **720-73** were prepared by methods similar to the methods used to prepare compounds 619-635 (see, Example 13). Physical data for compounds **720-73** is listed in Table 29.

1H), 7.82 (t, 1H), 8.05 (d, 1H), 8.55 (d, 1H), and 9.05 ppm (d, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid, O-2,6-dichlorobenzyl oxime(688c) was synthesized via methods used to prepare **308d** to afford **800**, ^{1}H NMR (CD_3OD) δ 2.2 (s, 6H), 2.58-2.83 (m, 2H), 3.28 (s, 3H), 3.29-3.34 (m, 1H), 3.68-3.80 (m, 2H), 3.95-4.05 (dd, 1H), 4.38-4.48 (dd, 1H), 4.82-5.00 (m, 2H), 5.26-5.36 (m, 2H), 7.22-7.65 (m, 10H).

(3*S*)-2-Oxo-(2,4-dimethylthiazo-5-yl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(800) was synthesized via methods used to prepare **696a-1** to afford 204 mg of **800** as a yellow solid, ^{1}H NMR($CDCl_3$)(mixture of diastereomers) δ 1.70(s, 1H), 2.40-2.80(m, 7H), 2.80-2.90(m, 0.5H), 2.95-3.05(m, 0.5H), 3.30-3.35(m, 0.5H), 3.45-3.55(m, 0.5H), 3.55-3.65(m, 1H), 3.80-4.05(m, 2H), 4.30-4.50(m, 2H), 4.55-4.65(m, 1H), 4.75-4.95(m, 3H), 5.45(s, 0.5H), 5.55(d, 0.5H), 6.70(d, 0.5H), 6.90(d, 0.5H), 7.15-7.80(m, 10H)

(3*S*)-3-[(3*S*)-2-Oxo-3-(2,4-dimethylthiazo-1-oyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(801) was synthesized via methods used to prepare **2002** from **2001** to afford **801**.

(m, 3H), 7.65 (m, 1H), 7.75 (t, 1H), 7.85 (t, 1H), 8.00 (d, 1H), 8.55 (d, 1H), and 9.05 ppm (d, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-2,3,4,5-tetrahydro-7-chloro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(696-2) was synthesized via methods used to prepare **2002** from **2001** to afford 250 mg of **696-2**as a white solid, ^{1}H NMR(CD_3OD) δ 2.40-2.55(m, 1H), 2.60-2.75(m, 1H), 3.80-4.00(m, 2H), 4.05(d, 1H), 4.20-4.35(m, 1H), 4.45-4.65(m, 3H), 4.80-5.10(m, 2H)

(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(699a-1) was synthesized via methods used to prepare **655** to afford **699a-1** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 (ddd, 1H), 2.90 (ddd, 1H), 3.25 (s, 3H), 3.28 (s, 3H), 3.80 (bt, 2H), 3.95 (bm, 2H), 4.25 (dd, 1H), 4.45-4.90 (m, 3H), 5.60 (d, 1H), 7.05- 7.40 (m, 8H), 7.50 (bm, 1H), 7.65- 7.85 (m, 2H), 8.45 (d, 1H), 9.1 (m, 1H), and 9.35 ppm (m, 1H)

(3*S*)-3-[(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(699a-2) was synthesized via methods used to prepare **2002** from **2001** to afford **699a-2** ^{1}H NMR (500 MHz, CD_3OD) δ 2.51 (m, 1H), 2.70 (dt, 1H), 3.31 (bs, 3H), 3.90 (bdt, 1H), 3.95 (bm, 1H), 4.05 (d, 1H), 4.35 (m, 1H), 4.50 (d, 1H), 4.60 (dd, 1H), 4.65 (dt, 1H), 4.80 (m, 1H), 5.05 (m, 1H), 7.35- 7.48 (m, 3H), 7.65 (bm, 1H), 7.75 (t,

(d, 1H), 7.10 (d, 1H), 7.20-7.35 (m, 3H), 7.40- 7.50 (m, 1H), 7.60- 7.85 (m, 3H), 8.40 (dd, 1H), 9.10 (m, 1H), and 9.30 pp (m, 1H).

(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-chloro-1H-1,5-benzodiazepine-1-acetamide(696a-2) was synthesized via methods used to prepare **677**, to afford 204 mg of **696a-2** as a white solid,with the exception that the reduction of the nitro- group was done as follows: To a solution of the nitro compound (7.2 g, 20 mmol) in MeOH was added NH_4Cl (2.1 g, 39 mmol) and Zn (17 g, 260 mmol). The resulting mixture was heated to reflux 1 hour after which it was cooled and filtered through celite. The filtrated was concentrated *in vacuo* then treated with cold 1N HCl to afford 3.6 g of a pale red solid. ^1H NMR($CDCl_3$) δ 1.85(s, 1H), 2.45(d, 0.5H), 2.50-2.65(m, 0.5H), 2.80-2.90(m, 0.5H), 2.90-3.00(m, 0.5H), 3.45(s, 0.5H), 3.55-3.75(m, 1H), 3.85-4.15(m, 2H), 4.25(d, 1H), 4.40-4.65(m, 2H), 4.70-4.80(m, 0.5H), 4.85-5.15(m, 3H), 5.40(s, 0.5H), 5.60(d, 0.5H), 7.00(d, 0.5H), 7.15-7.90(m, 12.5H), 8.35-8.45(m, 1H), 9.00-9.10(m, 1H), 9.25-9.40(m, 1H)

(3*S*)-3-[(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(696-1) was synthesized via methods used to prepare **2002** from **2001** to afford 140 mg of **696-1** as a white solid, ^1H NMR (500 MHz, CD_3OD) δ 2.50 (m, 1H), 2.70 (m, 1H), 3.85 (d, 1H), 3.95 (m, 1H), 4.10 (d, 1H), 4.35 (m, 1H), 4.50-4.60 (m, 2H), 4.80 (bm, 1H), 5.00 (m, 1H), 7.40- 7.48

4.85 (m, 1H), 4.88-5.1 (m, 2H), 5.45 (s, 0.5H), 5.55-5.65 (d, 0.5H), 6.85-6.92 (m, 1H), 7.02-7.13 (m, 2H), 7.24-7.55(m, 9H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(689b-1) was synthesized via methods used to prepare **2002** from **2001** to afford **689b-1**, ^{1}H NMR (CD_3OD) δ 2.18 (s, 6H), 2.36-2.47 (m, 1H), 2.6-2.72 (m, 1H), 3.34 (s, 3H), 3.66-3.88 (m, 2H), 3.95-4.05 (m, 1H), 4.2-4.78 (m, 5H), 4.9 (m, 1H), 7.3-7.41 (m, 2H), 7.48 (s, 2H), 7.5-7.63 (m, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(699) was synthesized via methods used to prepare **2002** from **2001** to afford **699** as a white solid, ^{1}H NMR (500 MHz, CD_3OD) δ 2.50 (m, 1H), 2.70 (m, 1H), 3.25 (s, 3H), 3.80 (bd, 1H), 3.90 (bd, 1H), 4.00 (bd, 1H), 4.30 (m, 1H), 4.50-4.70 (m, 3H), 4.80-4.85 (bt, 1H), 5.00 (bm, 1H), 7.40-7.55 (m, 5H), 7.70 (bm, 1H), 7.85 (bm, 1H), 8.00 (bm, 1H), 8.55 (bd, 1H), and 9.05 ppm (bd, 1H).

(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-hydroxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(696a-1) was synthesized via methods used to prepare **656** to afford **800** as a yellow solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 (ddd, 1H), 2.85 (ddd, 1H), 3.70-3.80 (m, 2H), 3.95 (bm, 1H), 4.05 (d, 1H), 4.30 (d, 1H), 4.40-4.60 (m, 4H), 4.70- 5.05 (m, 4H), 5.55

1H), 7.3-7.85(m, 11H), 7.9(t, 1H), 8.2(d, 1H), 8.6(m, 1H), 9.3(m, 1H).

(3*S*)-3-[(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid(698) was synthesized via methods used to prepare **653** to afford 225 mg of **698** ^{1}H NMR (500 MHz, CD_3OD) δ 2.4(m, 1H), 2.6(m, 1H), 3.9(m, 1H), 4.2(m, 1H), 4.3-4.7(m, 4H), 5.1(m, 1H), 7.3-7.5(m, 4H), 7.6-7.8(m, 2H), 7.8(m, 2H), 8.2(d, 1H), 8.5(d, 1H), 9.0(d, 1H).

(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-methoxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(699a) was synthesized via methods used to prepare **655** to afford 820 mg of **699a** as a tan solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (ddd, 1H), 2.90 (ddd, 1H), 3.20 (s, 3H), 3.25 (s, 3H), 3.70 (t, 1H), 3.90 (m, 2H), 4.20 (dd, 1H), 4.60 (m, 2H), 4.70-5.00 (m, 5H), 5.55 (d, 1H), 7.00 (d, 1H), 7.20-7.50 (m, 7H), 8.45 (dd, 1H), 9.0 (dd, 1H), and 9.35 ppm (dd, 1H).

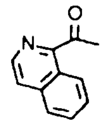
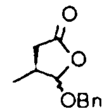
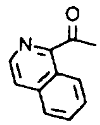
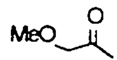
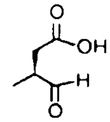
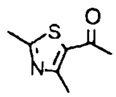
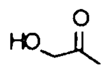
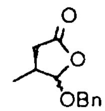
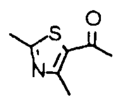
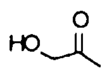
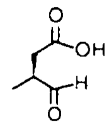
(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-7-fluoro-1H-1,5-benzodiazepine-1-acetamide(688b-1) was synthesized via methods used to prepare **655** to afford 600 mg of **688b-1**, ^{1}H NMR ($CDCl_3$; mix. of diastereomers) δ 2.21 (s, 3H), 2.28 (s, 3H), 2.42-2.50 (m, 0.5 H), 2.58-2.65 (m, 0.5H), 2.83-2.91 (m, 0.5H), 2.98-3.1 (m, 0.5H), 3.18 (s,1.5H), 3.22 (s, 1.5H), 3.72-3.78 (d, 1H), 3.78-3.9 (m, 2H), 4.08-4.15 (d, 1H), 4.5-4.69 (m, 3H), 4.7-

2.6-2.7 (m, 0.5H), 2.8-2.9 (m, 0.5H), 2.92-3.03 (m, 0.5H), 3.55-3.8 (m, 2H), 3.92-4.02 (d, 1H), 4.25-4.3 (d, 0.5H), 4.37-4.42 (d, 0.5H), 4.43-4.48 (m,0.5H), 4.55-4.65 (m, 1.5H) 4.7-5.12 (m, 5H), 5.44 (s, 0.5H), 5.58-5.63 (d, 0.5H), 6.95-8.1 (m, 13H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro4-aminobenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxobutyric acid (697) was synthesized via methods used to prepare **2002** from **2001** to afford 140 mg of **697**, ^{1}H NMR (CD_3OD) δ 238-2.5 (m,1H), 2.55-2.75 (m, 1H), 3.68-3.9 (m, 3H), 3.95-4.03 (m, 1H), 4.2-4.3 (m, 1H), 4.4-4.7 (m, 4H), 7.35-7.8 (m, 6H).

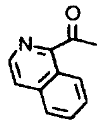
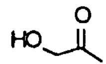
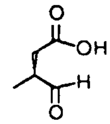
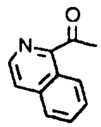
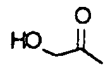
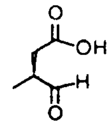
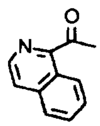
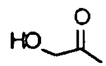
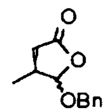
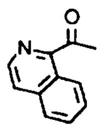
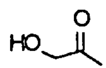
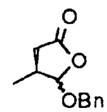
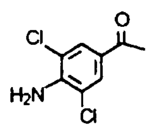
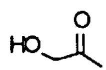
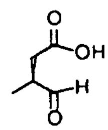
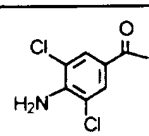
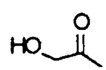
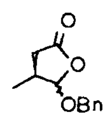
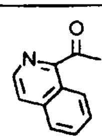
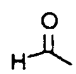
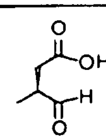
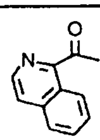
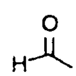
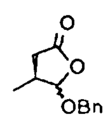
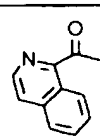
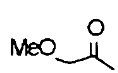
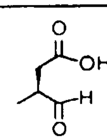
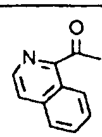
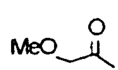
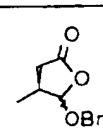
(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-acetoxy-3-butenoic acid ethyl ester(684a), was synthesized by the methods used to prepare **2100j** to afford **684a**, ^{1}H NMR (500 MHz, $CDCl_3$ mixture of diastereomers) δ 1.3 (s, 9H), 1.8(s, 3H), 2.1(s, 3H), 2.15(s, 3H), 2.3(s, 6H), 3.3-3.5(m, 3H), 3.65(s, 3H), 3.9(m, 1H), 4.1(d, 1H), 4.3(d, 1H), 4.6-4.8(m, 3H), 5.0(m, 1H), 6.7(s, 1H), 7.0(d, 1H), 7.1(d, 1H), 7.2-7.5(m, 6H).

(3*S*)-2-Oxo-3-isoquinolin-1-oylamino-5-formyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(698a) was synthesized via methods used to prepare **652** to afford 795 mg of **698a** ^{1}H NMR (500 MHz, $CDCl_3$ mixture of diastereomers) δ 2.8(m, 2H), 4.0(m, 1H), 4.5-4.8(m, 4H), 5.2(m, 1H), 5.5(s, 1H), 5.75(d,

CIP#	R^4	R^3	R^5	R^1
699a-1			F	
699a-2			F	
800			H	
801			H	

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4,4-diethoxybutyric acid ethyl ester(690a-1), was synthesized by the methods used to prepare **690a** and **2100b** to afford **690a-1**, ^{1}H NMR($CDCl_3$) δ 1.15(t, 6H), 1.3(t, 3H), 2.25(s, 6H), 2.60(d, 2H), 3.50(m, 2H), 3.70(m,4H), 4.05(m, 2H), 4.15(m, 2H), 4.30(d, 1H), 4.45(m, 1H), 4.50(d, 1H), 4.55(d, 1H), 4.70(t, 1H), 5.05(m, 1H), 5.30(s, 1H), 6.70(d, 1H), 7.10(d, 2H), 7.30-7.50(m, 7H)

(3*S*)-2-Oxo-3-(3,5-dichloro-4-aminobenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*) 2-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide(697a) was synthesized via methods used to prepare **677** to afford 840 mg of **697a**, ^{1}H NMR ($CDCl_3$) δ 1.78 (br. s, 2H), 2.48-2.58 (d, 0.5H),

CIP#	R^4	R^3	R^5	R^1
696-1			F	
696-2			Cl	
696a-2			Cl	
696a-1			F	
697			H	
697a			H	
698			H	
698a			H	
699			H	
699a			H	

Example 33

Compounds **684a**, **688b-1**, **688c**, **689b-1**, **690a-1**, **696-1**, **696-2**, **696a-2**, **696a-1**, **697**, **697a**, **698**, **698a**, **699**, **699a**, **699a-1**, **699a-2**, **800** and **801** were prepared as described below.

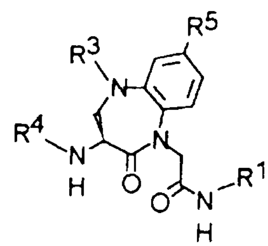
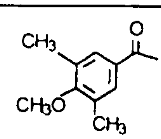
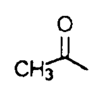
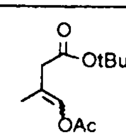
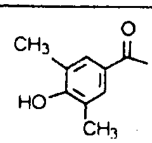
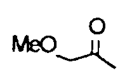
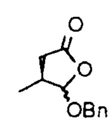
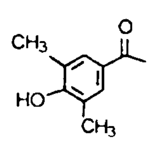
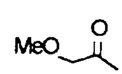
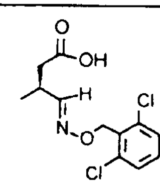
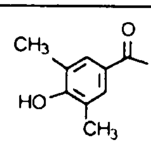
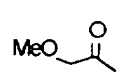
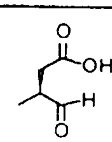
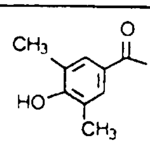
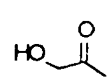
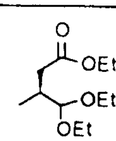


Table 28

CIP#	R^4	R^3	R^5	R^1
684a			H	
688b-1			F	
688c			H	
689b-1			F	
690a-1			H	

Example 32

Table 27

Compound	UV-Visible Ki (nM)	Cell PBMC avg. IC50 (nM)	Whole human blood IC50 (nM)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
688c	200				
689b-1	3.5		2700		
696-1	0.5				
696-2	0.5				
697	1.8		5000		
698	18		13500		
699	1.1				
699a-2					
720	2.7				
721	1.3		5000		
722	5		5000		
723	2.3		2000		
724	2		1800		
725	3.7		3000		
726	300				
727	50		2300		
728	300				
729	28		2800		
730	90		8000		
731	150				
732	5		1800		
733	5		1500		
734	9		6000		
735	6		10000		

3.05(m, 1H), 3.9(d, 1H), 4.2(m, 1H), 4.3(d, 1H), 4.7-5.0(m, 3H), 5.25(m, 1H), 5.7(s, 1H), 5.9(d, 1H), 7.5(d, 2H), 7.7-7.9(m, 3H), 8.0(t, 1H), 8.2(m, 2H), 8.75(d, 1H), 9.35(d, 1H).

(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-(2*RS*-cyclopentyloxy-5-oxo-tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696d) was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696d**. ^{1}H NMR ($CDCl_3$) δ 0.9(t, 1H), 1.2(t, 1H), 1.3-1.45(m, 2H), 1.6-1.8(m, 4H), 2.45(m, 1H), 2.8(m, 1H), 3.0(m, 1H), 3.4(q, 1H), 3.5(d, 1H), 4.0(m, 2H), 4.2-4.3(m, 2H), 4.55(d, 1H), 4.65(m, 1H), 4.9(m, 1H), 5.05(m, 1H), 5.4(s, 1H), 5.5(d, 1H), 6.8(d, 1H), 7.3-7.9(m, 6H), 8.5(d, 1H), 9.05(d, 1H), 9.4(d, 1H).

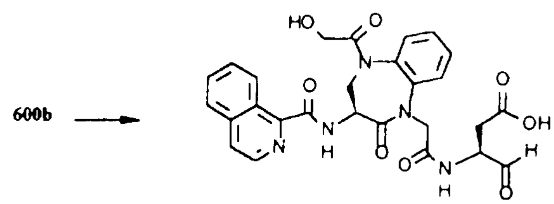
(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2*R*,3*S*)-phenethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (696e) was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696e**. ^{1}H NMR ($CDCl_3$) δ 1.2(t, 1H), 2.4(m, 1H), 2.8(m, 2H), 3.6(d, 1H), 3.7(q, 1H), 4.0(m, 2H), 4.3(d, 2H), 4.65(m, 1H), 4.85(t, 1H), 5.0(m, 1H), 5.35(d, 1H), 6.5(d, 1H), 7.15-7.85(m, 8H), 8.45(d, 1H), 9.05(d, 1H), 9.4(d, 1H).

(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (696a) was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696a**. ^{1}H NMR ($CDCl_3$) δ 0.95(t, 2H), 1.25(t, 1H), 1.4(m, 2H), 1.55(m, 1H), 2.55(m, 1H), 2.85(m, 1H), 2.95(dd, 1H), 3.15(m, 1H), 3.55(m, 1H), 3.9(m, 2H), 4.35(t, 1H), 4.4-4.55(m, 2H), 4.75(m, 1H), 4.8-5.05(m, 2H), 5.45(s, 1H), 5.55(d, 1H), 6.85(d, 1H), 7.15(d, 1H), 7.2-7.5(m, 5H), 7.6-7.8(m, 3H), 8.45(d, 1H), 9.05(d, 1H), 9.35(d, 1H).

(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-ethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696b) was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696b**. ^{1}H NMR ($CDCl_3$) δ 0.9(m, 3H), 1.15(q, 3H), 1.15(m, 1H), 1.65(m, 1H), 2.5(m, 1H), 2.8(m, 1H), 2.95-3.0(m, 2H), 3.6(m, 2H), 3.7-3.85(m, 4H), 4.0(m, 2H), 4.3(m, 1H), 4.55(m, 1H), 4.65(m, 1H), 4.85-4.95(m, 1H), 5.05(m, 1H), 5.35(s, 1H), 5.45(d, 1H), 6.85(d, 1H), 7.25(d, 1H), 7.35-7.85(6H), 8.85(dd, 2H), 9.05(m, 1H), 9.35(dd, 2H).

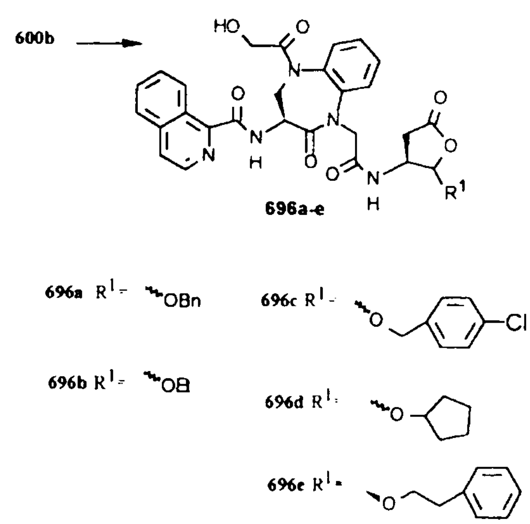
(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-[2*RS*-(4-chlorobenzyl)oxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-carboxamide (696c) was synthesized from **600b** via methods used to prepare **690a** from **600b** to afford **696c**. ^{1}H NMR (CD_3OD) δ 1.25(t, 1H), 1.65(q, 1H), 1.9(m, 1H), 2.9(m, 1H),

(2) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm). Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.



696

(3*S*)-3-[(3*S*)-2-Oxo-3-(isoquinolin-1-oyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (696) was synthesized from **600b** by the method used to prepare **691a** from **600b** to afford **696**. ^{1}H NMR (CD_3OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.75(d, 1H), 3.95(q, 1H), 4.05(d, 1H), 4.3(m, 1H), 4.45-4.65(m, 2H), 5.05(m, 1H), 7.5-7.6(m, 3H), 7.7(t, 1H), 7.8(t, 1H), 7.98(t, 1H), 8.55(d, 1H), 9.1(d, 1H).



Step E. (910-922) Resin **906** was acylated with a solution of 0.4M carboxylic acid and 0.4M HOBT in N-methypyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.25 mL) and the reaction was shaken for 2 hr at room temperature. The resin was washed with N-methylpyrrolidone (1 X 1 mL), dimethylformamide (4 X 1 mL), 50% methanol in dichloromethane (5 X 1 mL) and dried in air. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H_2O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (2 X 1 mL), the combined filtrates were added to cold 1:1 ether:hexane (35 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in acetonitrile (0.5 mL) and H_2O (0.5 mL) and filtered through 0.45 micron microcentrifuge filters. The compound was purified by semi-preparative RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (10% - 50%) containing 0.1% TFA (v/v) over 30 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **910-922**.

Analytical HPLC methods:

(1) Waters DeltaPak C18, 300Å (5μ, 3.9 X 150 mm). Linear acetonitrile gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

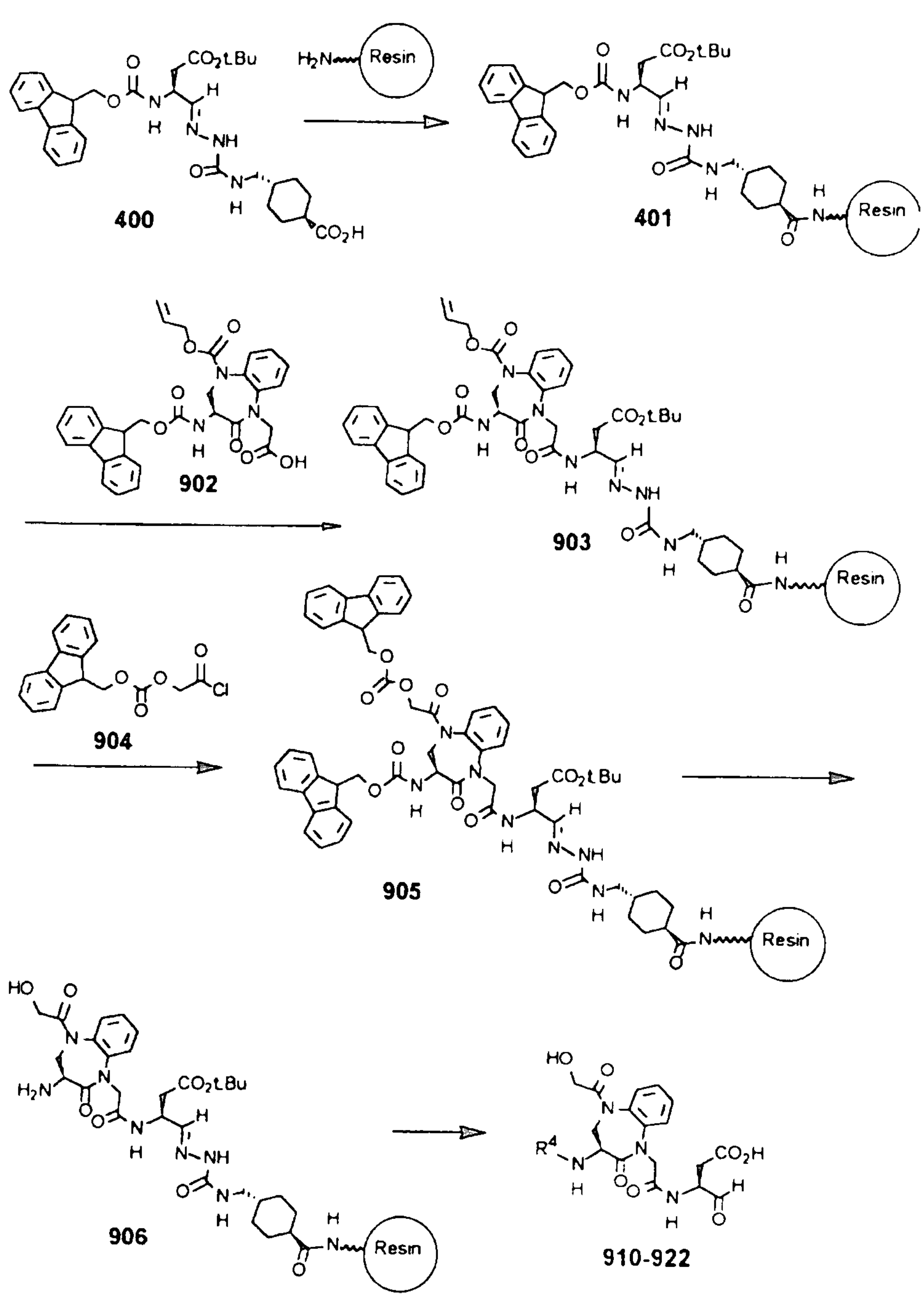
dimethylacetamide (4 X 20 mL) and dichloromethane (4 X 20 mL), and dried under nitrogen purge. Resin substitution was performed as described for **401** and determined to be 0.169 mmol g^{-1}.

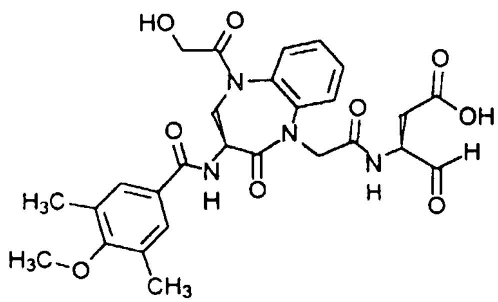
Step C. Synthesis of 905. Resin **903** (7.54 g, 1.27 mmol) and dimedone (2.19 g, 15.6 mmol) were placed in a 100 mL round bottomed flask and freshly distilled anhydrous tetrahydrofuran (60 mL) was added. Tetrakis(triphenylphosphine)palladium (0) (0.32 g, 0.28 mmol) was added and the nitrogen blanketed, sealed reaction was agitated for 15 h on a wrist action shaker. The resin was filtered, washed with dimethylacetamide (4 X 20 mL), dichloromethane (4 X 20 mL) and dimethylacetamide (1 X 20 mL). Sufficient dimethylacetamide was added to the resin to obtain a slurry followed by pyridine (1.5 mL, 18.5 mmol) and a solution of **904** (5.5 mmol) in dichloromethane (10 mL). The reaction was shaken under nitrogen for 8 h, then filtered. The resin was washed with dimethylacetamide (5 X 20 mL) and dichloromethane (5 X 20 mL).

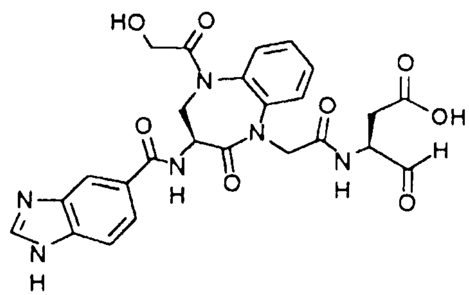
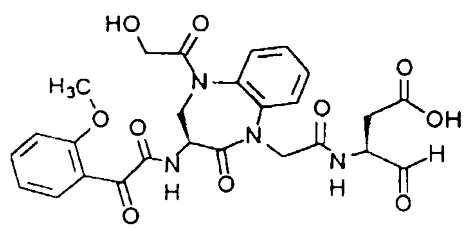
Step D. Synthesis of 906. This compound was prepared from resin **905** (0.24 g, 0.038 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (3 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 10 min followed by fresh reagent (1 mL) for 20 min to yield resin **906**. The resin was washed with dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL).

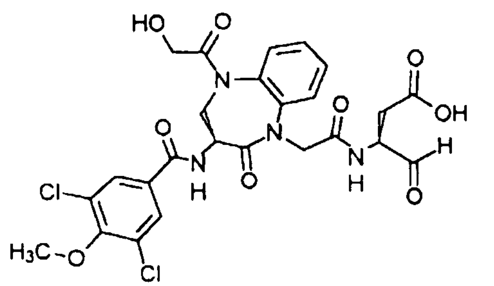
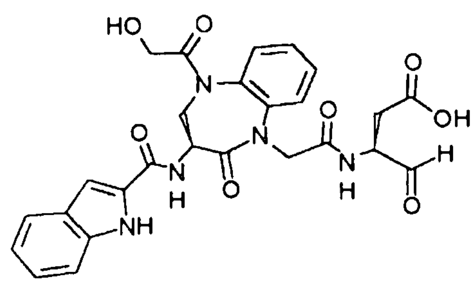
Step A. Synthesis of 401. TentaGel S® NH_2 resin (0.25 mmol/g, 6.8 g) was placed in a glass shaker vessel and washed with dimethylacetamide (3 X 20 mL). To a solution of **400** (1.70 g, 2.9 mmol, prepared from (3S) 3-(fluorenylmethyloxycarbonyl)-4-oxobutryic acid t-butyl ester according to A.M. Murphy et. al. J. Am. Chem. Soc., 114, 3156-3157 (1992)) in dimethylacetamide (15 mL) was added O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 1.09 g, 2.9 mmol), and DIEA (1.0 mL, 5.7 mmol). The solution was added to the resin, followed by dimethylacetamide (5 mL). The reaction mixture was agitated for 3 h at room temperature using a wrist arm shaker. The resin was isolated by suction filtration and washed with dimethylacetamide (6 X 20 mL). A sample of resin (7.4 mg) was thoroughly washed with 50% methanol in dichloromethane and dried under suction. Deprotection of the Fmoc group using 20% piperidine in dimethylacetamide (10.0 mL) and UV analysis of the solution revealed a substitution of 0.19 mmol g^{-1}.

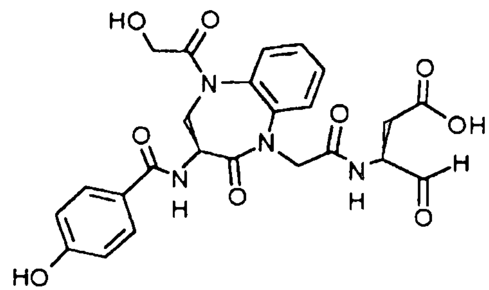
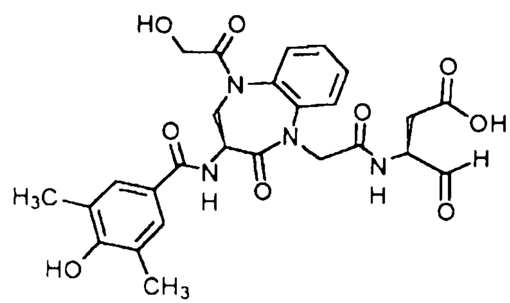
Step B. Synthesis of 903. Resin **401** was deprotected with 20% (v/v) piperidine/dimethylacetamide (20 mL) for 10 min (shaking) and then for 10 min with fresh piperidine reagent (20 ml). The resin was then washed with dimethylacetamide (6 X 20 ml). A solution of **902** (1.52 g, 2.81 mmol) was treated with HBTU (1.07 g, 2.83 mmol) and DIEA (1.0 mL, 5.7 mmol) and transferred to the resin, followed by dimethylacetamide (5 mL). The reaction mixture was agitated for 2.5 h at room temperature using a wrist arm shaker. The resin was isolated by suction filtration and washed with

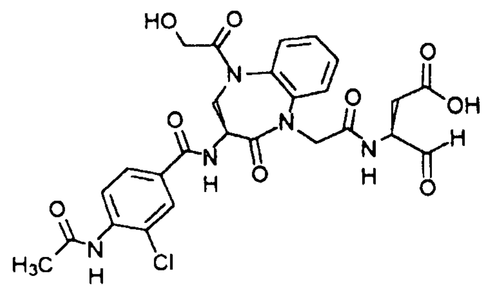
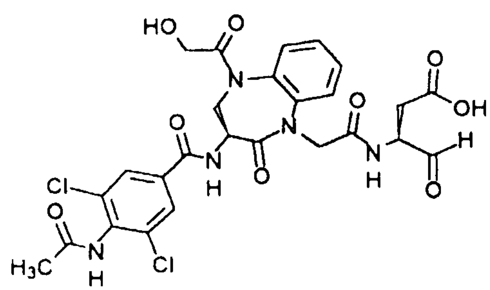

CO2tBu
H2N
Resin
400
401
902
903
904
905
906
910-922
HO
H2N
R4
CO2H
CO2H

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
922/694		C27H30N4O9	554.56	10.024 (2) 99%	578.8

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
920		C25H24N6O8	536.51	5.494 (2) 98%	560.6
921		C26H26N4O10	554.52	7.827 (2) 96%	579.1

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
918		C25H24Cl2N4O9	595.40	11.817 (2) 99%	619.3
919		C26H25N5O8	535.52	9.709 (2) 91%	559.7

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
916/691b		C24H24N4O9	512.48	6.331 (2) 98%	537
917/691a		C26H28N4O9	540.53	8.114 (2) 99%	564.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
914		C26H26ClN5O9	587.98	7.815 (2) 99%	612.2
915		C26H25Cl2N5O9	622.42	7.490 (2) 98%	647

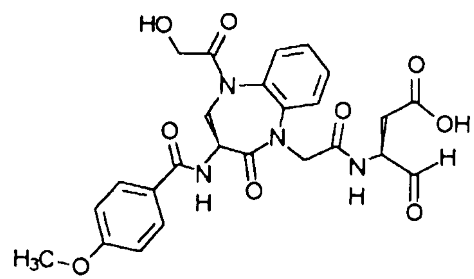
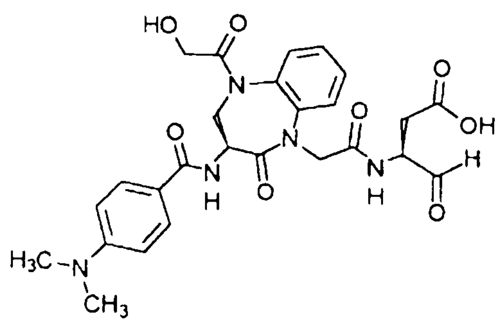
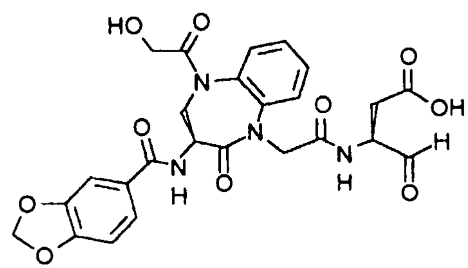
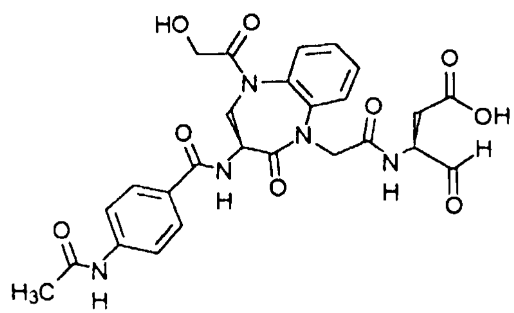
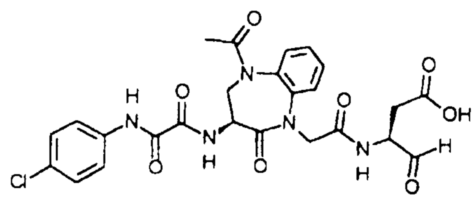
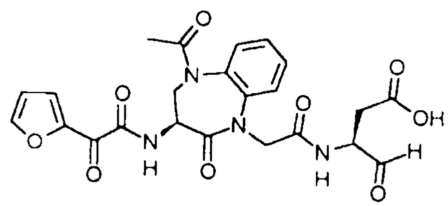
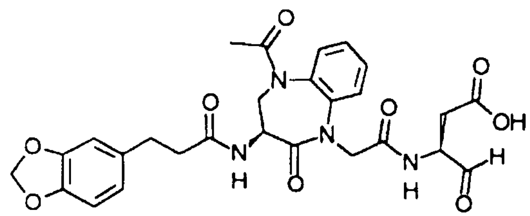
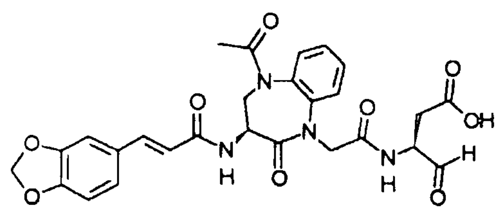
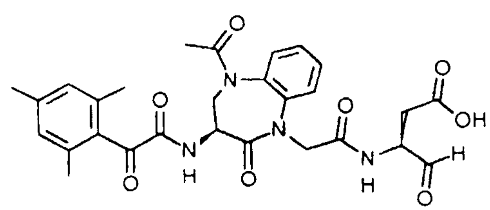
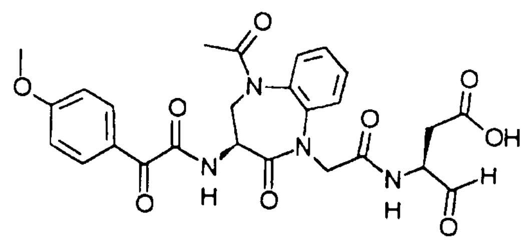
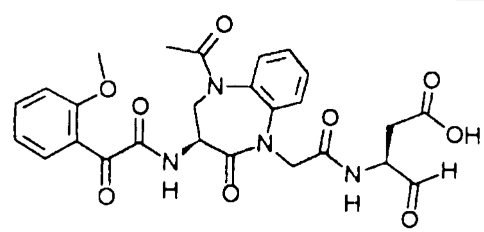
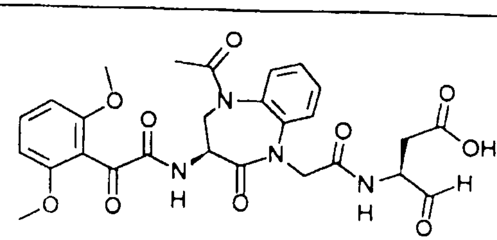
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
912		C25H26N4O9	526.51	8.317 (2) 99%	550.7
913		C26H29N5O8	539.55	6.588 (2) 99%	563.5

Table 26

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
910		C25H24N4O10	540.49	8.172 (2) 99%	564.4
911		C26H27N5O9	553.53	6.949 (2) 99%	577.5

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
710		C25H24ClN5O8	557.95	12.406 (2) 98%	582.2
711		C23H22N4O9	498.45	13.072 (1) 99%	521.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
707		C27H28N4O9	552.55	15.952 (1) 98%	575.9
708		C27H26N4O9	550.53	10.731 (2) 93%	574.6
709		C28H30N4O8	550.57	13.192 (2) 95%	574

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
704		C26H26N4O9	538.52	10.475 (2) 96%	562.1
705		C26H26N4O9	538.52	14.260 (1) 72%	562.1
706		C27H28N4O10	568.55	14.836 (1) 97%	592.4

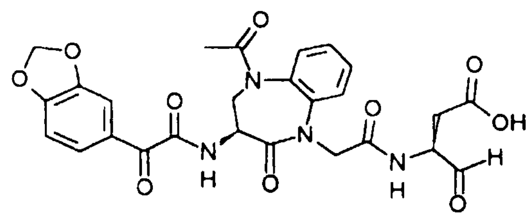
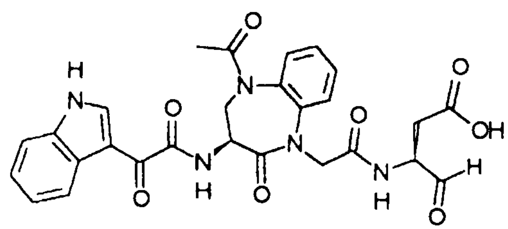
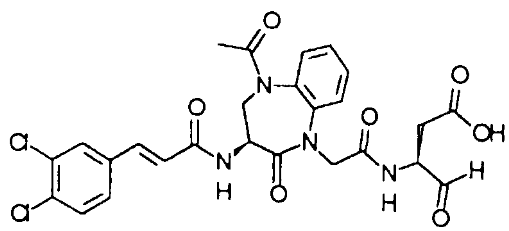
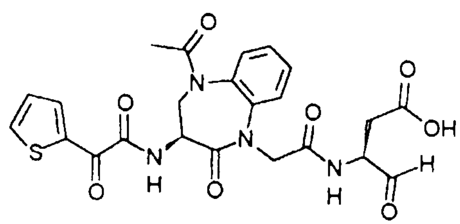
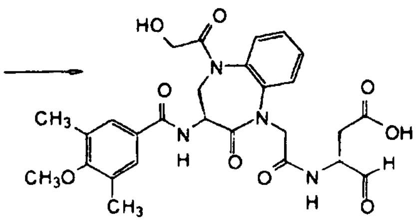
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
702		C26H24N4O10	552.50	15.855 (1) 98%	575.9
703		C27H25N5O8	547.53	10.315 (2) 97%	572.1

Table 25

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
700		C26H24Cl2N4O7	575.41	14.061 (2) 97%	600
701		C23H22N4O8S	514.52	15.589 (1) 97%	538.8

691c →



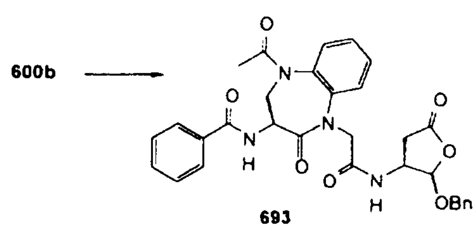
694

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (694), was synthesized from **691c** by the method used to prepare **2002** from **2001** to afford 380 mg of **694** as a white solid, ^{1}H NMR (CD_3OD) δ 2.25(s, 6H), 2.45(m, 1H), 2.65(m, 1H), 3.65(m, 5H), 4.0(d, 1H), 4.28(m, 1H), 4.55(d, 2H), 4.95(m, 1H), 7.4-7.6(m, 6H).

Compounds **700-711** were prepared by methods similar to the methods used to prepare compounds **619-635** (see, Example 13). Physical data for compounds **700-711** is listed in Table 25.

Compounds **910-915** and **918-921** were prepared as described below. Physical data for these compounds is listed in Table 26.

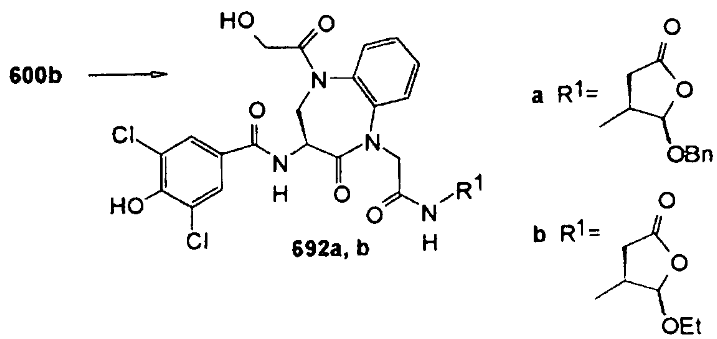
(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-ethoxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (692b), was synthesized from **600b** via methods used to prepare **661** from **600b**, excluding steps used to make **604d** from **603d**, using instead the method to prepare **688a** from **687a** to afford 207 mg of **692b**, ^{1}H NMR (CD_3OD) δ 1.05(t, 3H), 1.15(t, 3H), 2.45(d, 1H), 2.55(m, 1H), 2.7(m, 1H), 3.55(m, 2H), 3.6-3.75(m, 5H), 4.0(dd, 2H), 4.3(d, 1H), 4.4-4.7(m, 5H), 5.25(s, 1H), 5.5(d, 1H), 7.25-7.6(m, 4H), 7.85(s, 2H).



693

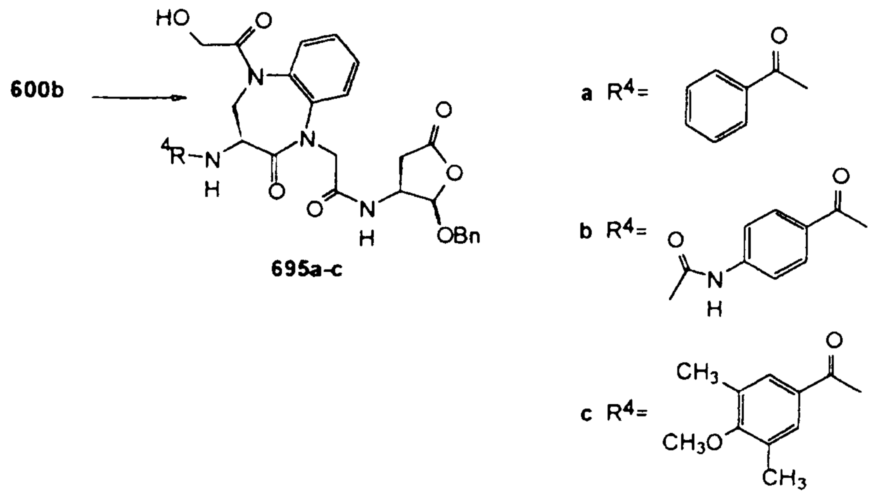
(3*S*)-2-Oxo-3-benzoylamino-5-acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (693), was synthesized from **600b** via methods used to prepare **688a** from **600b** to afford 30 mg of **693**, ^{1}H NMR (CD_3OD) δ 1.7(s, 3H), 1.8(s, 3H), 2.51(d, 1H), 2.6(m, 1H), 2.85(m, 1H), 3.0(m, 1H), 3.75(br. d, 2H), 4.0-4.1(dd, 2H), 4.5-5.0(m, 6H), 5.45(s, 1H), 5.55(s, 1H), 7.15-7.85(m, 14H).

(3*S*)-2*RS*-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-(2-benzyloxy-5-oxo-tetrahydrofuran-3-yl)-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (695c), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 840 mg of **695c**, ^{1}H NMR($CDCl_3$) δ 2.23(s, 3H), 2.26(s, 3H), 2.45-2.62(m, 1H), 2.8-2.9(dd, 0.5H), 2.9-3.05(dd, 0.5H), 3.45-3.63(m, 1H), 3.64(s, 1.5H), 3.68(s, 1.5H), 3.78-4.05(m, 2H), 4.2-4.33(m, 1H), 4.4-4.63(m, 2H), 4.65-4.94(m, 2H), 4.95-5.1(m, 1H), 5.45(s, 0.5H), 5.5-5.6(d, 0.5H), 6.9-6.95(d, 1H), 7.25-7.7(m, 12H).



692a, b

(3*S*)-2-Oxo-3-(3,5-dichloro4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (692a), was synthesized from **600b** via methods used to prepare **661** from **600b**, excluding steps used to make **604d** from **603d**, using instead the method to prepare **688a** from **687a** to afford 854 mg of **692a** , ^{1}H NMR (CD_3OD) δ 2.45(d, 1H), 2.6(m, 1H), 2.7(m, 1H), 3.0(m, 1H), 3.5-3.7(m, 4H), 4.0(q, 2H), 4.45(m, 3H), 4.55(m, 4H), 5.35(s, 1H), 5.6(d, 1H), 7.2-7.5(m, 9H), 7.85(s, 2H).



(3*S*)-2-Oxo-3-benzoylamino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (695a), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 75 mg of **695a**, ^{1}H NMR (CD_3OD) δ 2.2(s, 6H), 2.45(m, 1H), 2.6(m, 1H), 3.65(m, 1H), 3.75(d, 1H), 4.0(d, 1H), 4.28(m, 1H), 4.5(m, 3H), 7.4-7.6(m, 6H).

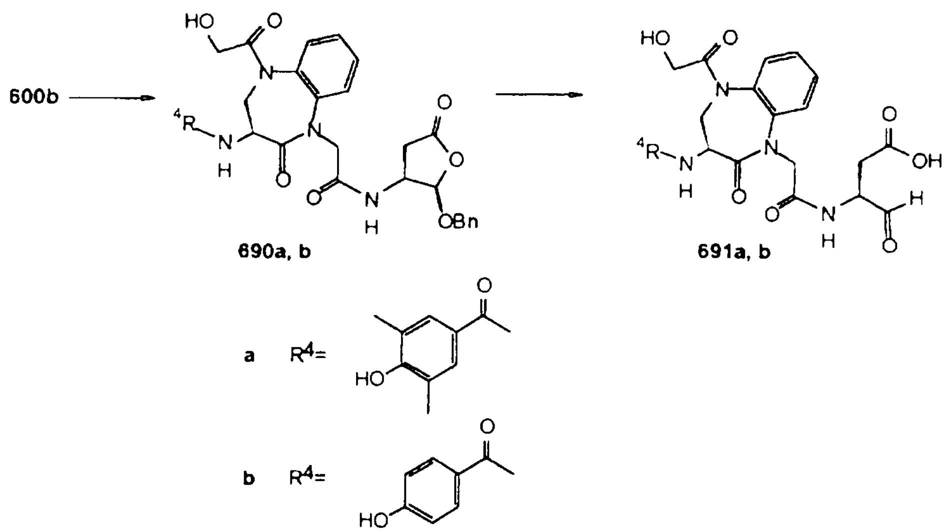
(3*S*)-2-Oxo-3-(4-acetamidobenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (695b), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 880 mg of **695b**, ^{1}H NMR ($CDCl_3$) δ 2.1(s, 3H), 2.25-2.5(m, 2H), 2.8-2.92(m, 0.5H), 3.15-3.2(m, 0.5H), 3.45-3.6(m, 2H), 3.75-3.95(m, 2H), 4.15-4.25(m, 1H), 4.35-4.6(m, 2H), 4.6-4.88(m, 3H), 5.22(s, 0.25H), 5.33(s, 0.25H), 5.52-5.58(d, 0.5H), 7.15-7.45(m, 9.5H), 7.5-7.75(m, 5H), 8.3-8.35(m, 0.5H), 9.08-9.18(m, 1H).

(CD_3OD) δ 2.49(d, 1H), 2.65(d, 1H), 2.66(d, 1H), 2.85(d, 1H), 2.87(d, 1H), 3.05(dd, 1H), 3.35(br. s, 1H), 3.72(br. s, 2H), 4.01(m, 2H), 4.45(br. m, 1H), 4.6(m, 1H), 4.7(m, 1H), 4.8(m, 1H), 4.95(br. s, 2H), 5.65(d, 1H), 6.8(d, 2H), 7.2-7.35(br. m, 3H), 7.45(m, 2H), 7.75(d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (691a), was synthesized from **690a** by the method used to prepare **2002** from **2001** to afford 560 mg of **691a** as a white solid, ^{1}H NMR (CD_3OD) δ 2.15(s, 6H), 2.45(m, 1H), 2.65(m, 1H), 3.55(m, 1H), 3.7(d, 1H), 4.0(d, 1H), 4.25(m, 1H), 4.5-4.6(m, 3H), 7.3-7.5(m, 6H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(4-hydroxybenzoyl)amino-5-hydroxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (691b), was synthesized from **690b** by the method used to prepare **2002** from **2001** to afford 410 mg of **691b** as a white solid, ^{1}H NMR (CD_3OD) δ 2.5(m, 1H), 2.65(m, 1H), 3.75(m, 1H), 3.8(d, 1H), 4.05(d, 1H), 4.25(m, 1H), 4.5(m, 1H), 4.6(m, 1H), 4.95(br. s, 2H), 6.8(d, 2H), 7.45(m, 2H), 7.6(m, 2H), 7.75(d, 2H).

2.7(m, 1H), 3.3(s, 3H), 3.7-3.85(m, 2H), 4.05(dd, 1H), 4.3(m, 1H), 4.6(m, 2H), 7.45-7.4(m, 2H), 7.5(s, 2H), 7.55(m, 2H).



(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (690a), was synthesized from **600b** via methods used to prepare **676** from **600b**, **688a** from **687a**, then **677** from **676** to afford 863 mg of **690a** as a white solid, ^{1}H NMR (CD_3OD) δ 2.2(s, 6H), 2.45(d, 0.5H), 2.6-2.9(m, 1H), 3.05(dd, 0.5H), 3.65-3.85(m, 2H), 3.95-4.1(m, 1H), 4.35-5.0(m, 7H), 5.35(s, 0.5H), 5.65(d, 0.5H), 7.2-7.4(m, 4H), 7.4-7.7(m, 7H).

(3*S*)-2-Oxo-3-(4-hydroxybenzoyl)amino-5-hydroxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (690b), was synthesized from **600b** via methods used to prepare **677** from **600b** to afford 200 mg of **690b**, ^{1}H NMR

NMR (CD_3OD) δ 2.55(dd, 1H), 2.7(dd, 1H), 3.0(m, 1H), 3.6(m, 1H), 3.75(d, 1H), 3.9-4.0(m, 2H), 4.3-4.45(m, 3H), 4.5-4.6(m, 3H), 4.7(m, 2H), 5.35(s, 1H), 5.55(d, 1H), 7.1-7.5(m, 4H), 7.85(s, 2H).

(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (688b), was synthesized from **687b** by the method used to prepare **688a** from **687a** to afford 960 mg of **688b** as an off-white solid, ^{1}H NMR (CD_3OD) δ 2.6(dd, 1H), 2.7(dd, 1H), 3.0(dd, 1H), 3.2(s, 3H), 3.7(m, 3H), 3.9(m, 2H), 4.4-4.5(m, 2H), 4.6(m, 3H), 5.35(s, 1H), 5.55(d, 1H), 7.25(m, 2H), 7.4-7.5(m, 4H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (689a), was synthesized from **688a** by the method used to prepare **2002** from **2001** to afford 184 mg of **689a** as a white solid, ^{1}H NMR (CD_3OD) δ 2.45(m, 1H), 2.6(m 1H), 3.3(s, 3H), 3.7-3.85(m, 2H), 4.0(d, 1H), 4.3(m, 1H), 4.5-4.6(m, 3H), 7.3-7.6(m, 4H), 7.85(s, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (689b), was synthesized from **688b** by the method used to prepare **2002** from **2001** to afford 412 mg of **689b** as a white solid, ^{1}H NMR (CD_3OD) δ 2.5(m, 1H),

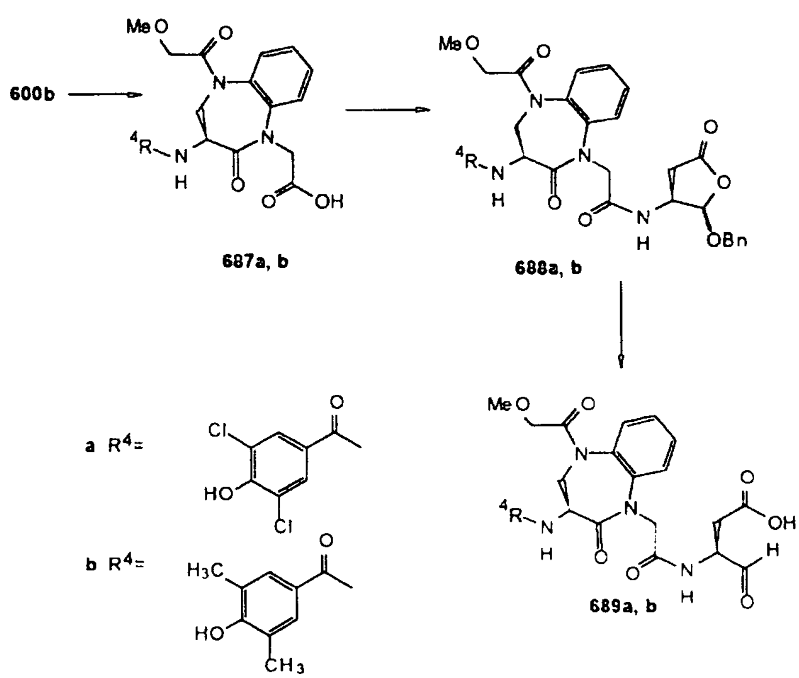
(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (687a), was synthesized from **600b** using methods similar to those used for preparing **654** from **600b** to afford 1.6 g of **687a**.

(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (687b), was synthesized from **600b** using methods similar to those used for preparing **654** from **600b** to afford 1.1 g of **687b**.

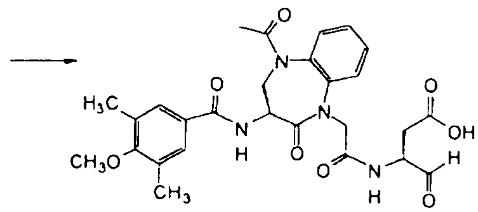
(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-methoxyacetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (688a). To a solution of (3*S*,2R,S)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Biorg. Med. Chem. Lett., 2, pp. 613-618 (1992)) (1.13 g, 1.2 equiv) in CH_2Cl_2 was added triphenylphosphine (423 mg, 0.5 equiv), dimethylbarbituric acid (1.26 g, 2.5 equiv), and tetrakistriphenylphosphine palladium (0) (373 mg, 0.1 equiv). After 5 minutes the reaction mixture was cooled via ice-bath then added a solution of **687a** in DMF (1.6 g, 1 equiv), HOBT (480 mg, 1.1 equiv), and EDC (681 mg, 1.1 equiv). The resulting mixture was allowed to stir at ambient temperature. After 16 hours the reaction mixture was poured into $NaHSO_4$ and extracted twice with EtOAc. The organic layer was washed with $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography (SiO_2, 20% to 100% EtOAc in CH_2Cl_2) afforded 880mg of **688a** as an off-white solid, ^1H

benzodiazepine-1-acetamide (685), was synthesized from **600b** by the methods used to prepare **676** from **600b** to afford 165 mg of **685**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(3-chloro-4-aminobenzoyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (686). To a solution of **685** (165 mg, 0.21 mmol) in THF was added a solution of TBAF (1M, 0.21 mL). The product was isolated by filtration after precipitation from reaction mixture. Reverse phase chromatography (10% to 80% MeCN in water/ 0.1% TFA) afforded 25 mg of **686** as a white solid, ^{1}H NMR (CD_3OD) δ 2.37-2.42 (m), 2.59-2.70 (m), 3.60-3.89 (m), 4.01 (d), 4.20-4.31 (m), 4.42-4.70 (m), 4.80-5.05 (m), 6.79 (d), 7.32-7.65 (m), 7.81 (s).



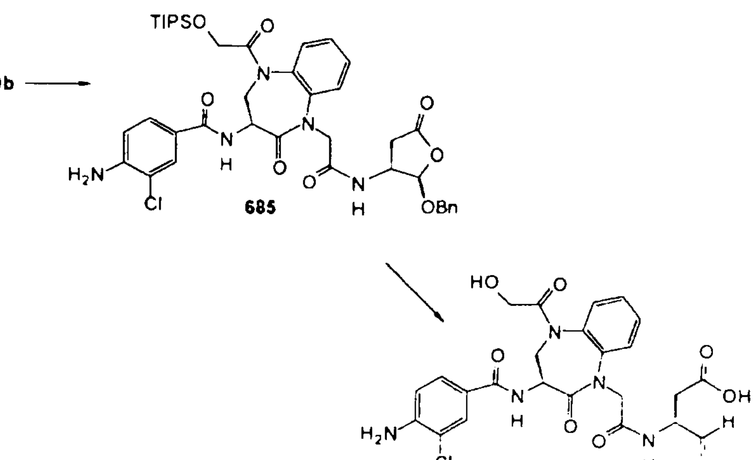
600b



684

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-methoxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (684), was synthesized from **600b** by the method used to prepare **605d** from **600b** to afford 72 mg of **684** as a white solid, ^{1}H NMR (CD_3OD) δ 1.9(s, 3H), 2.25(s, 6H), 2.45(m, 1H), 2.6(m, 1H), 3.3(s, 1H), 3.7(s, 3H), 4.25(m, 1H), 4.45-4.6(m, 3H), 7.4(br. s, 2H), 7.55(br. d, 4H).

600b

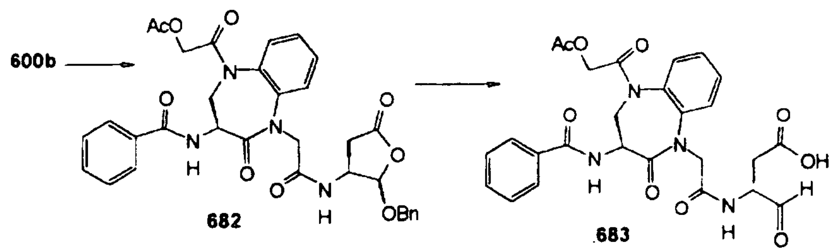


685

686

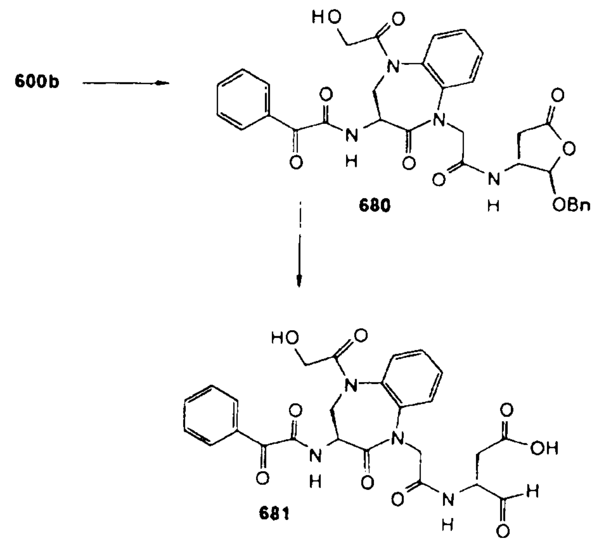
**(3*S*)-2-Oxo-3-(3-chloro-4-aminobenzoyl)amino-5-(2-triisopropylsilyloxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-

4.85(br. s, 2H), 7.3(br. m, 2H), 7.4-7.7(m, 5H), 8.15(d, 2H).



(3*S*)-2-Oxo-3-benzoylamino-5-(2-acetoxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (682), was synthesized from **600b** by the methods used to prepare **655** from **600b** to afford 495 mg of **682** as a white solid, ^{1}H NMR ($CDCl_3$) δ 2.00(s, 3H), 2.05(s, 3H), 2.47(d, 1H), 2.58(dd, 1H), 2.85(dd, 1H), 2.89(dd, 1H), 3.9(m, 2H), 4.05-4.15(m, 2H), 4.19(dd, 1H), 4.45(m, 2H), 4.55-5.05(m, 8H), 5.55(d, 1H), 6.85(d, 1H), 7.15(d, 1H), 7.25-7.55(m, 10H), 7.75(d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(2-acetoxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (683), was synthesized from **682** by the method used to prepare **2002** from **2001** to afford 82 mg of **683** as a white solid, ^{1}H NMR (CD_3OD) δ 2.1(s, 3H), 2.5(m, 1H), 2.68(m, 1H), 3.8(m, 1H), 4.29(dd, 1H), 4.31(m, 1H), 4.45(d, 1H), 4.55(d, 1H), 4.6(d, 1H), 4.72(d, 1H), 4.95(br. s, 2H), 7.45(br. m, 2H), 7.52-7.65(br. m, 5H), 7.88(d, 2H).



(3*S*)-2-Oxo-3-benzoylformylamino-5-(2-hydroxy)acetyl-N-(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (680), was synthesized from **600b** by the methods used to prepare **677** from **600b** to afford 140 mg of **680** as a white solid, ^{1}H NMR (CDCl$_3$) δ 2.31(d, 1H), 2.4(dd, 2H), 2.75(dd, 2H), 2.85(dd, 1H), 3.36(br. s, 1H), 3.45(br. s, 1H), 3.6(br. t, 2H), 3.82(br. m, 2H), 3.95(br. d, 2H), 4.35(m, 2H), 4.42(d, 1H), 4.55(m, 1H), 4.70(d, 1H), 4.82(br. s, 2H), 5.5(d, 1H), 6.91(d, 1H), 7.25(br. m, 5H), 7.35-7.46(br. m, 3H), 7.5-7.6(m, 2H), 8.15(br. d, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylformylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (681), was synthesized from **680** by the method used to prepare **678** from **677** to afford 45 mg of **681** as a grey solid, ^{1}H NMR (CD$_3$OD) δ 2.5(m, 1H), 2.7(dt, 1H), 3.65-3.85(br. m, 3H), 4.05(m, 1H), 4.3(m, 1H), 4.5-4.7(br. m, 3H),

(3*S*)-2-Oxo-3-(1,6-dimethoxybenzoylformyl)amino-5-(2-triisopropylsilyloxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (676), was synthesized from **675** by the method used to prepare **213e** to afford 166 mg of **676** as a white solid.

(3*S*)-2-Oxo-3-(1,6-dimethoxybenzoylformyl)amino-5-(2-hydroxy)acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (677). A solution of TBAF (6 mL, 3 mmol) in HOAc (0.46 mL, 8 mmol) was added to **676** (0.213 g, 0.256 mmol). After 16 hours the reaction mixture was poured into EtOAc and washed twice with $NaHCO_3$, once with brine then dried over $MgSO_4$ and concnetrated *in vacuo* to afford 139 mg of **677** as a solid, ^1H NMR ($CDCl_3$) δ 2.4(d, 1H), 2.5(dd, 1H), 2.8(dd, 1H), 2.92(dd, 1H), 3.15(m, 2H), 3.55-3.65(m, 2H), 3.72(s, 6H), 3.92(m, 1H), 4.05(m, 1H), 4.3(m, 1H), 4.42(d, 1H), 4.6(dd, 1H), 4.65-4.8(m, 2H), 4.88(d, 1H), 5.55(d, 1H), 6.55(m, 2H), 6.75(d, 1H), 7.25-7.55(m, 8H), 7.75(m, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethoxybenzoylformyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (678), was synthesized by the method used to prepare **667** from **666** to afford 54 mg of **678** as a white solid, ^1H NMR (CD_3OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.5(m, 2H), 3.75(br. s, 6H), 4.05(d, 1H), 4.3(m, 1H), 4.51-4.6(m, 2H), 4.8(br. m, 2H), 6.7(d, 2H), 7.4-7.5(br. m, 3H), 7.6-7.65(br. m, 2H).

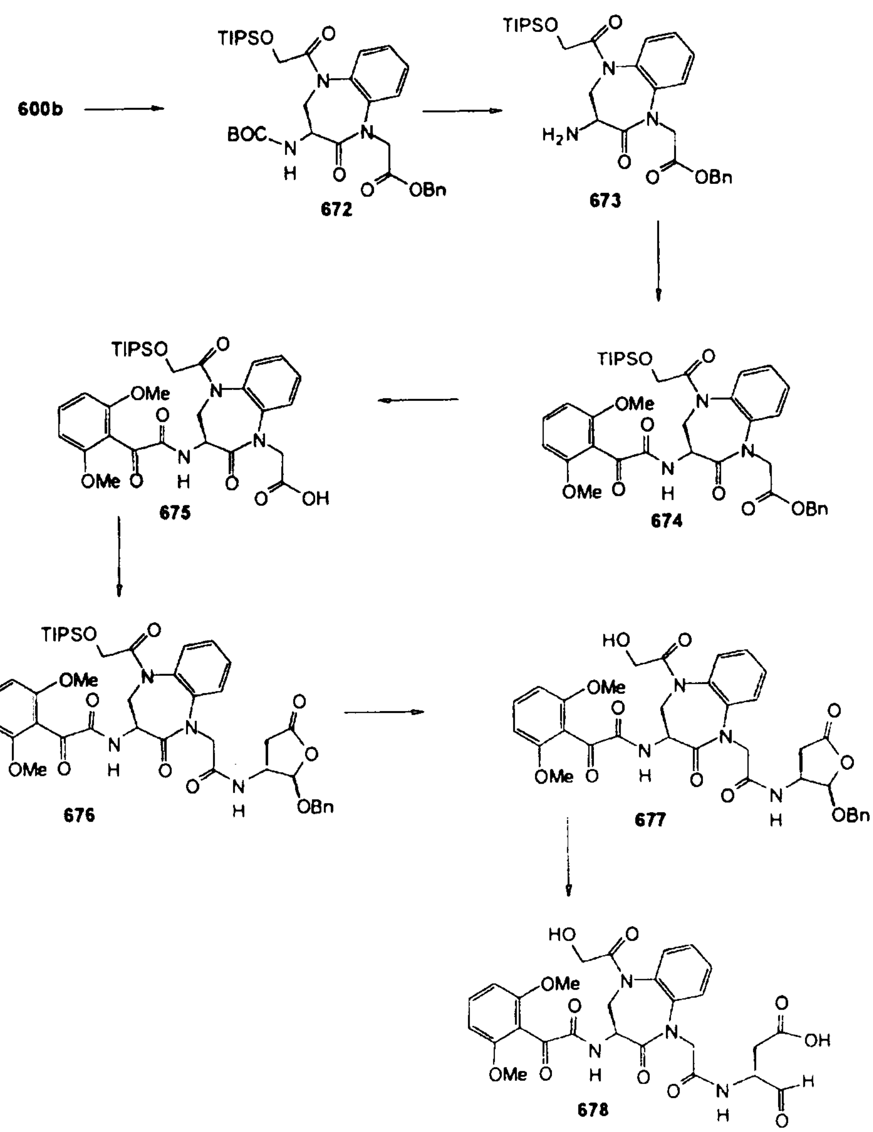
(3*S*)-2-Oxo-3-*tert*-butoxycarbonylamino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (672), was synthesized from **600b** by method 1 used to prepare **602n** from **600b** using **665** to afford 1.08 g of **672**.

(3*S*)-2-Oxo-3-amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (673). To a solution of **672** (1.08 g, 1.69 mmol) in CH_2Cl_2 was added 2,6-lutadine (0.8 mL) then TMSOTf (1 mL, 5.1 mmol). After 1 hour, the reaction mixture was poured into $NaHCO_3$ and extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated *in vacuo* to a small volume that was used directly for the next reaction.

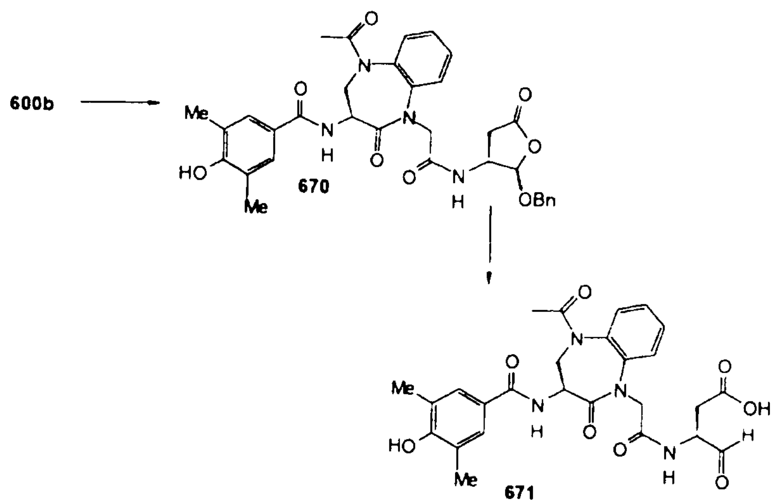
(3*S*)-2-Oxo-3-(1,6-dimethoxybenzoyl formyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzylester (674), was synthesized from **673** by the method used to prepare **602b** to afford 0.91 g of **674**.

(3*S*)-2-Oxo-3-(1,6-dimethoxybenzoyl formyl)amino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (675). A solution of **674** (0.365 g, 0.5 mmol) in MeOH was stirred with 1N NaOH (1.2 mL, 1.2 mmol). After 16 hours the reaction mixture was concentrated *in vacuo* then dissolved in water and washed twice with ether. The aqueous layer was acidified with 1N HCl and the product extracted with EtOAc, dried over $MgSO_4$ and concnetrated *in vacuo* to afford 337 mg of **675** as a solid.

2.4-2.5(m, 1H), 2.6-2.75(m, 1H), 3.65-3.75(m, 2H), 4.2-4.3(m, 2H), 4.45-4.6(m, 3H), 7.35-7.6(m, 4H), 7.5(s, 2H).



white solid, ^{1}H NMR (CD_3OD) δ 1.9(s, 3H), 2.4-2.7(m, 2H), 3.6-3.7(m, 2H), 3.9(s, 3H), 4.2-4.4(m, 2H), 4.4-4.6(m, 3H), 7.4-7.8(m, 4H), 7.9(s, 2H).



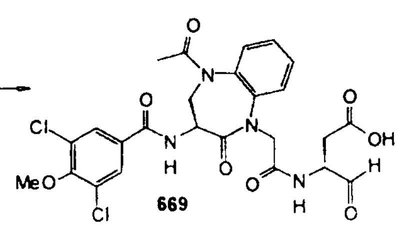
(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (670), was synthesized from **600b** by the methods used to prepare **655** from **600b** to afford 218 mg of **670** as a white solid, ^{1}H NMR (CD_3OD) δ 1.7, 1.75(2s, 3H), 2.15, 2.2(2s, 6H), 2.4-2.5(m, 1H), 2.6-2.75(m, 1H), 3.65-3.75(m, 2H), 4.2-4.3(m, 2H), 4.45-4.6(m, 3H), 7.35-7.6(m, 4H), 7.5(s, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dimethyl-4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (671), was synthesized from **670** by the methods used to prepare **2002** from **2001** to afford 253 mg of **671** as a white solid, ^{1}H NMR (CD_3OD) δ 1.9(s, 3H), 2.25(s, 6H),

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (667). To a solution of **666** (131 mg, 0.17 mmol) in tetrahydrofuran, cooled via ice-water bath, was added tetrabutylammonium fluoride (1M, 0.190 mL). After 2 hours the reaction mixture was poured into water, extracted twice with EtOAc, dried over $MgSO_4$ and concentrated *in vacuo* to afford 63 mg of **667** as a white solid.

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(2-hydroxy) acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (668), was synthesized from **667** by the methods used to prepare **605d** from **604d** to afford 48 mg of **668** as a white solid, ^{1}H NMR (CD_3OD) δ 2.45(m, 1H), 2.67(dddd, 1H), 3.78(d, 1H), 3.85(br. m, 1H), 4.05(d, 1H), 4.28(m, 1H), 4.5(m, 2H), 4.65(m, 1H), 4.95(br. s, 2H), 7.4-7.5(m, 4H), 7.52-7.65(m, 3H), 7.88(d, 2H).

600b ⟶



669

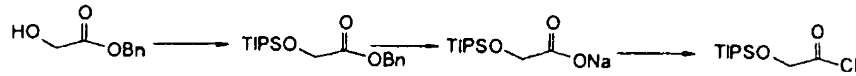
(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro-4-methoxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (669), was synthesized from **600b** by the methods used to prepare **605d** from **600b** to afford 63 mg of **669** as a

2-(Triisopropylsilyloxy)acetic acid benzyl ester (663). To a solution of benzyl glycolate (46.91g, 0.282 mol) and diisopropylethylamine (74 mLs, 0.423 mol) in CH_2Cl_2, cooled via water bath, was added a solution of TIPSOTf (95 g, 0.31 mol) in CH_2Cl_2. The resulting mixture was allowed to warm to ambient temperature then poured into water, washed twice with 10% aqueous $NaHSO_4$, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (SiO_2, 0 to 5% EtOAc in hexanes) afforded 71.6 g of **663**.

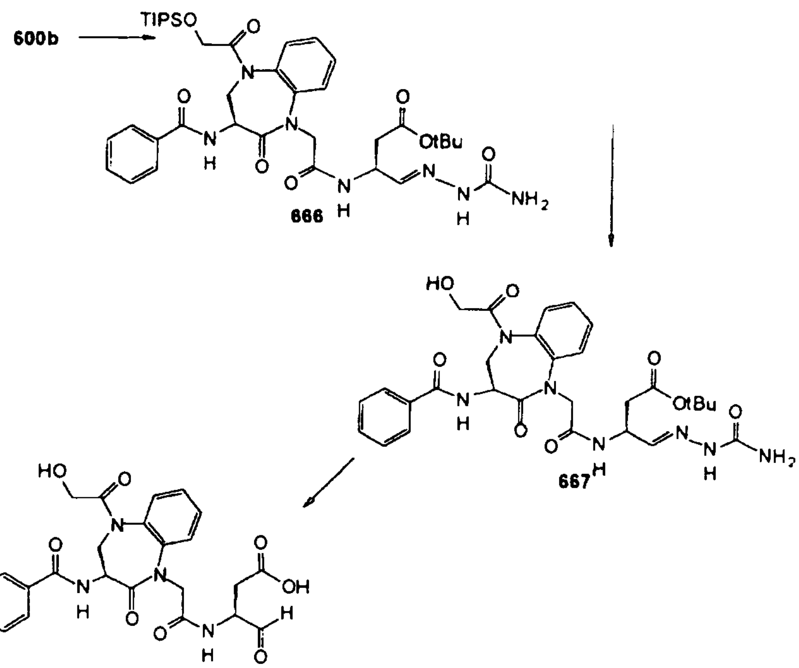
2-(Triisopropylsilyloxy)acetic acid (664). To a solution of **663** (0.4 g, 1.2 mmol) in EtOAc was added 10% Pd/C (33 mg). The resulting suspension was stirred under hydrogen atmosphere. After 15 hours, the reaction mixture was filterred through Celite and the filtrate concentrated *in vacuo* to afford 0.29 g of an oil. To a solution of this oil in 1,4-dioxane was added $NaHCO_3$ (0.5M, 2.4 mLs). The resulting solution was concentrated *in vacuo* from toluene to afford **664** as a waxy solid.

2-(Triisopropylsilyloxy)acetyl chloride (665), was synthesized from **664** by a method similar that used to prepare **643** to afford **665** as a crude product.

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylamino-5-(2-triisopropylsilyloxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (666), was synthesized from **600b**, using **665**, by methods used to prepare **604d** from **600b** to afford 131 mg of **666**.



663 664 665



668

from **600b**, using **659**, by methods used to prepare **604d** from **600b** to afford 453 mg of **660**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-hydroxy)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (661). A solution of **660** (423 mg) in MeOH:Et_2NH (1:1, v/v) was stirred at ambient temperature. After 10 minutes, the reaction mixture was concentrated *in vacuo* to a small volume. Precipitation by the addition of ether afforded 230 mg of **661**.

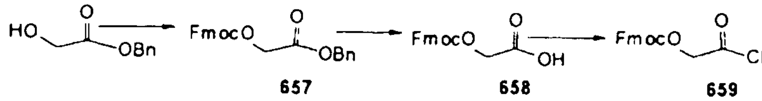
(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-hydroxy) acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (662), was synthesized from **661** by the methods used to prepare **605d** from **604** to afford 37 mg of **662** as a white solid, ^1H NMR (CD_3OD) δ 2.45(m, 1H), 2.7(m, 1H), 3.75(m, 1H), 3.9(d, 1H), 4.15(d, 1H), 4.35(m, 1H), 4.5(t, 2H), 4.7(dd, 1H), 7.4-7.6(m, 4H), 7.85(s, 2H).

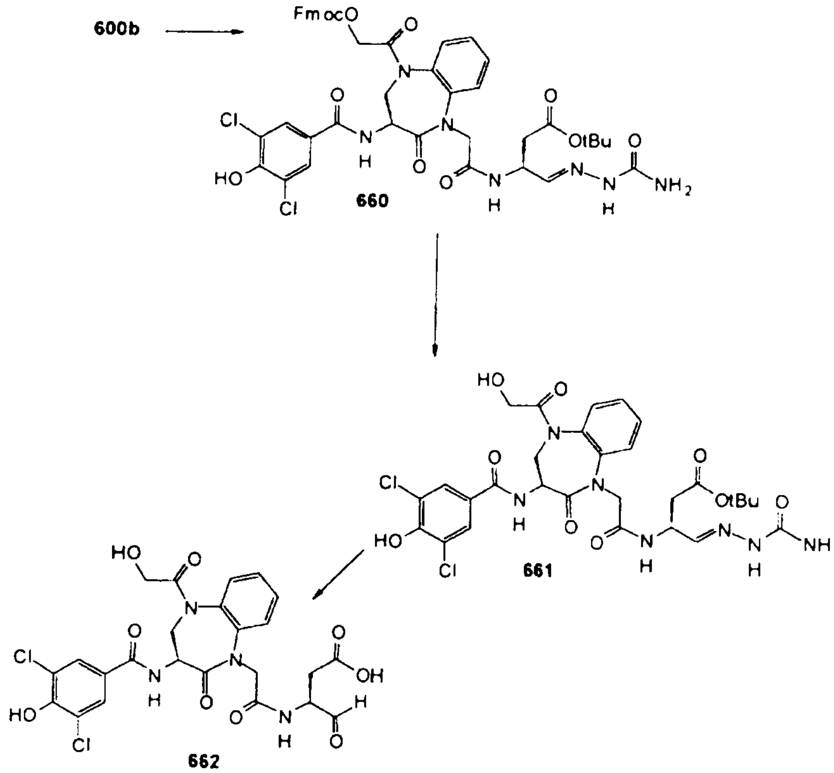
2-(Fluorenylmethoxycarbonyl)hydroxyacetic acid benzyl ester (657). To a solution of benzyl glycolate (6.0 g, 36.1 mmol) in CH_2Cl_2, cooled via ice-water bath, was added fluorenylmethoxy chloroformate (14 g, 1.5 equiv.) then diisopropylethylamine (9 mLs, 1.5 equiv.). After 1 hour, reaction mixture was poured into a saturated aqueaous solution of ammonium chloride and extracted with CH_2Cl_2, dried over Na_2SO_4 then concentrated *in vacuo*. The product was triturated from MeOH to obtain 2.2 g of **657** as a first crop of white solid.

2-(Fluorenylmethoxycarbonate) acetic acid (658). To a solution of **657** (2.2 g, 5.93 mmol) in tetrahydrofuran was added 5% Pd/C (220 mg). The resulting suspension was vigorously stirred under hydrogen atmosphere. After 90 min, the reaction mixture was filterred through Celite. The filtrate was poured into saturated aqueous $NaHCO_3$ and washed twice with EtOAc. The aqueous layer was then acidified and the product extracted twice with CH_2Cl_2, dried over Na_2SO_4 and concentrated *in vacuo* to afford 1.46 g (88%) of **658** as a white solid.

2-(Fluorenylmethoxycarbonate) acetyl chloride (659), was prepared from **658** by the method used to prepare **643** to afford **659** as a crude product.

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-(2-fluorenylmethoxycarbonate)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (660), was synthesized



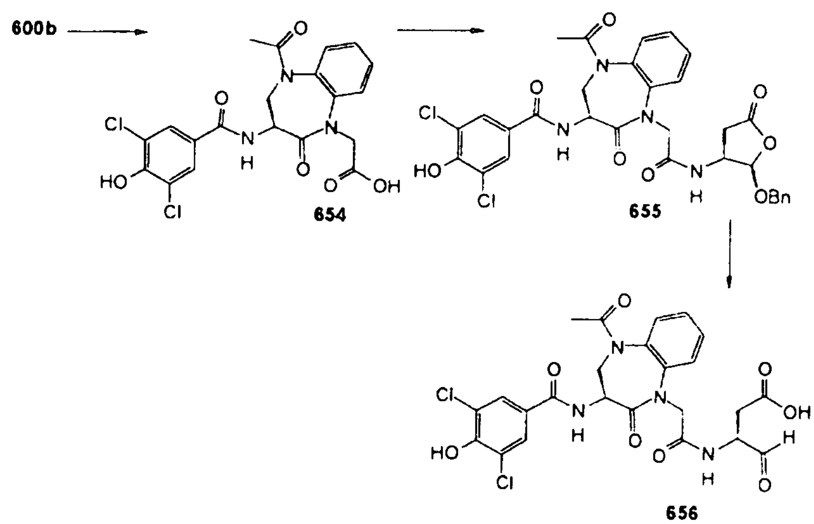


(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-acetyl-N-[(2*RS*,3*S*)-benzyloxy-5-oxo-tetrahydrofuran-3-yl]-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetamide (655), was synthesized from **654** using the method used to prepare **213e** to afford 304 mg of **655**, ^1H NMR (CD_3OD) δ 2.4(d, 1H), 2.6-2.75(m, 2H), 3.0(m, 1H), 3.45(m, 1H), 3.8(d, 1H), 4.0(t, 2H), 4.4(m, 2H), 4.5-4.55(m, 2H), 7.2-7.45(m, 4H), 7.85(s, 2H).

(3*S*)-3-[(3*S*)-2-Oxo-3-(3,5-dichloro, 4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (656), was synthesized from **655** using a method similar to that used to prepare **2002** from **2001** to afford 136 mg of **656** as a white solid, ^1H NMR (CD_3OD) δ 1.85(s, 3H), 2.5(m, 1H), 2.65(m, 1H), 3.7(m, 1H), 4.3(m, 1H), 4.55(m, 2H), 7.4-7.6(m, 4H), 7.85(s, 2H).

reagent obtained from reacting DMF with 3 equiv. of oxalyl chloride in a CH_2Cl_2 solution as R^3X, to afford 404 mg of **652**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (653), was synthesized from **652** by methods used to prepare **605d** from **602d** to afford 84 mg of **653** as a white solid, ^1H NMR (CD_3OD) δ 2.3(m, 1H), 2.55(dd, 1H), 3.75(br. s, 1H), 4.25-4.6(m 5H), 5.15(m, 1H), 7.2-7.45(m, 6H), 7.8-7.9(dd, 3H), 8.1(s, 1H), 8.2(m, 2H).



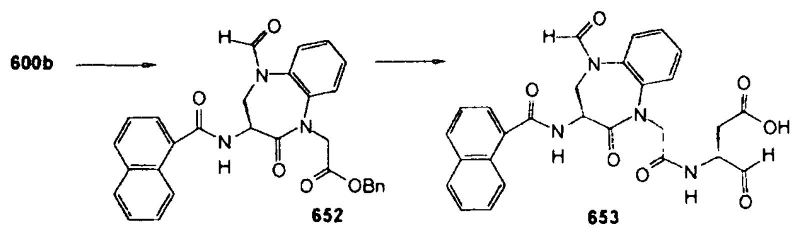
(3*S*)-2-Oxo-3-(3,5-dichloro-4-hydroxybenzoyl)amino-5-acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid (654), was synthesized from **600b** using methods similar to those used for preparing **603d** from **600b** to afford 775 mg of **654**.

synthesized from **647** by methods used to prepare **604d** from **602d** to afford 409 mg of **648**.

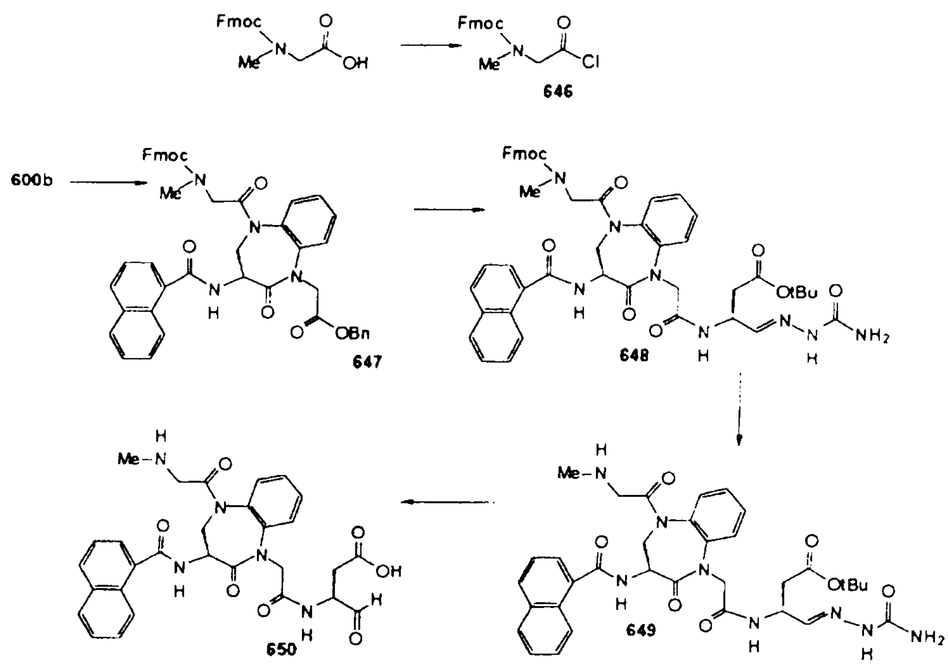
(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-(2-methyl amino) acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (649).

A solution of **648** (409 mg, 0.465 mmol) in MeCN:Et_2NH (4:1, v/v) was stirred at ambient temperature. After 45 minutes, the reaction mixture was concentrated *in vacuo*. Flash chromatography (SiO_2, 5% to 20% MeOH in CH_2Cl_2) afforded 241 mg of **649**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-(2-methyl amino) acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (650), was synthesized from **649** by methods used to prepare **605d** from **604** to afford 179 mg of **650** as a white solid, ^1H NMR (CD_3OD) δ 2.4-2.6(m, 2H), 2.7(s, 3H), 3.5(q, 1H), 3.8(m, 2H), 4.2-4.4(m, 2H), 4.3-4.45(m, 1H), 5.0-5.1(m, 2H), 7.4-7.7(m, 6H), 7.85-7.9(m, 2H), 8.2(m, 1H).



(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-formyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (652), was synthesized from **600b** by methods similar to those used to make **602n** from **600b**, using the



2-(*N*-Methyl, *N*-fluorenylmethoxycarbonyl)aminoacetyl chloride (646), was prepared from *N*-Fmoc-sarcosine by method used to make **643** to afford **646** as a crude product.

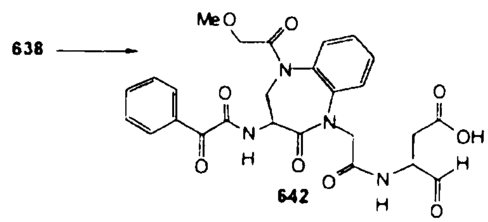
(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-[2-(*N*-methyl, *N*-fluorenylmethoxycarbonyl) amino]acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (647), was synthesized from **600b** by methods used to synthesize **602d** from **600b**, using **646** to afford 481 mg of **647**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-[2-(*N*-methyl, *N*-fluorenylmethoxycarbonyl)amino]acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid *tert*-butyl ester semicarbazone (648), was

(0.450 mLs, 5.1 mmol). After stirring 30 minutes at ambient temperature, the mixture was concentrated to afford **643** as a crude product.

(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-(2-acetamido)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid benzyl ester (644), was synthesized from **600b** by methods used to make **602d** from **600b** using **643** to afford 112 mg of **644**.

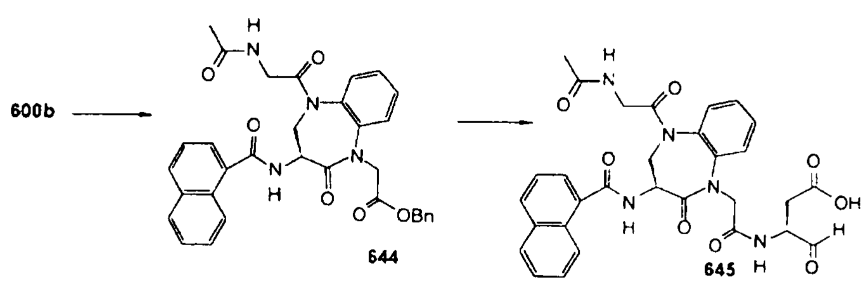
(3*S*)-3-[(3*S*)-2-Oxo-3-(1-naphthoyl)amino-5-(2-acetamido)acetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (645), was synthesized from **644** by methods used to make **605d** from **602d** to afford 43 mg of **645** as a white solid, ^{1}H NMR (CD_3OD) δ 1.95(s, 3H), 2.4(m, 1H), 2.65(m, 1H), 3.4(s, 1H), 3.55(m, 1H), 3.85(m, 1H), 4.05(d, 1H), 4.3(m, 1H), 4.4-4.6(m, 2H), 5.0(m, 1H), 7.4-7.7(m, 6H), 7.85-8.0(m, 2H).



638 642

(3*S*)-3-[(3*S*)-2-Oxo-3-benzoylformylamino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (642), was synthesized from **638** by similar methods used to make **605m** to afford 213 mg of **642**, ^{1}H NMR (CD_3OD) δ 2.5(m, 1H), 2.68(ddd, 1H), 3.25(s, 2H), 3.3(s, 3H), 3.78(m, 2H), 4.0(d, 1H), 4.3(m, 1H), 4.6(m, 2H), 4.85(br. s, 2H), 7.08-7.22(m, 2H), 7.35(m, 1H), 7.4-7.65(m, 4H), 7.7(dd, 1H), 8.1(dd, 1H).

643



600b 644 645

2-Acetamido-acetyl chloride (643). To a suspension of N-acetyl glycine (200 mg, 1.7 mmol) in CH_2Cl_2 (2.5 mLs) containing DMF (0.005 mLs) was added oxalyl chloride

(3*S*)-2-Oxo-3-amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (638), was synthesized from **600a** by methods similar to those used for making **602m** from **600a** to afford 2.4g of **638** as a white solid.

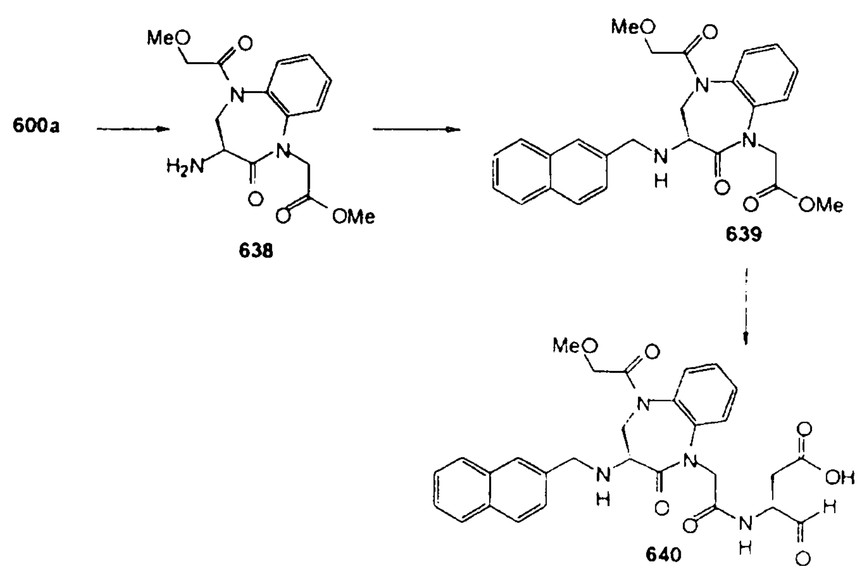
(3*S*)-2-Oxo-3-(2-naphthylmethylene)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetic acid methyl ester (639). To a solution of **638** (630 mg, 1.76 mmol) and 2-naphthylmethyl bromide (428 mg, 1.94 mmol) in CH_3CN was added K_2CO_3 (608 mg, 4.4 mmol). The resulting mixture was stirred at ambient temperature. After 18 hours, the reaction mixture was diluted with CH_2Cl_2, washed with water then brine, dried over Na_2SO_4 then concentrated in vacuo. Flash chromatography (SiO_2, 0 to 20% EtOAc/CH_2Cl_2) afforded 450mg of **639**.

(3*S*)-3-[(3*S*)-2-Oxo-3-(2-naphthylmethylene)amino-5-methoxyacetyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine-1-acetylamino]4-oxo-butyric acid (640), was synthesized by methods used to make **605v** from **602v** to afford 205 mg of **640** as a white solid, ^1H NMR ($CDCl_3$) δ 2.4-2.55(m, 1H), 2.65-2.8(m, 1H), 3.2(s, 3H), 3.72-3.78(m, 1H), 3.85-4.0(m, 2H), 4.22-4.28(d, 1H), 4.26-4.5(m, 4H), 4.58-4.75(m, 1H), 4.78-4.85(m, 1H), 5.0-5.08(t, 1H), 7.35-7.65(m, 7H), 7.85-8.02(m, 4H).

58%): mp. 124-32°C; IR (KBr) 3312, 2979, 1790, 1664, 1610, 1532, 1485, 1285, 1120, 1037, 932; ^{1}H NMR (D_6-DMSO) δ 10.39 (1H, s), 8.71 (0.5H, d), 8.43 (0.5H, d), 7.45 (1H, d), 7.36 (1H, s), 7.04 (1H, d), 6.12 (2H, s), 5.58 (0.5H, d), 5.34 (0.5H, s), 4.95-4.85 (1H, m), 4.70-4.52 (0.5H, m), 4.35-4.10 (1.5H, m), 3.95-3.50 (5H, m), 3.03 (0.5H, dd), 2.90-2.55 (1.5H, m), 2.46-2.20 (2H, m), 2.10-2.40 (4H, m), 1.16-1.13 (3H, 2 x t). Anal. Calcd for $C_{23}H_{27}N_5O_9 \cdot 0.6H_2O$: C, 52.29; H, 5.38; N, 13.26. Found: C, 52.53; H, 5.35; N, 12.78. MS (ES$^+$) 519 (M^+ + 2, 27%), 518 (M^+ + 1, 100), 472 (7), 374 (12), 373 (53), 345 (14), 149 (12).

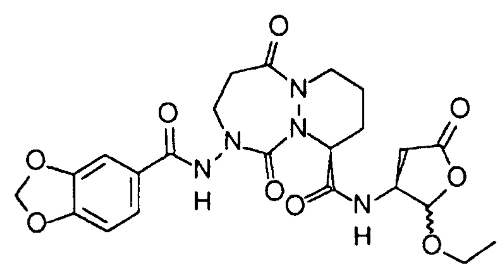
Example 31

Compounds **640**, **642**, **645**, **650**, **653**, **655**, **656**, **662**, **668**, **669**, **670**, **671**, **677**, **678**, **681**, **682**, **683**, **684**, **686**, **688a**, **688b**, **6891**, **689b**, **690a**, **690b**, **691a**, **691b**, **695a**, **695b**, **695c**, **692a**, **692b**, **693** and **694** were prepared as follows.



$C_{27}H_{34}N_8O_7S$: C, 52.76; H, 5.58; N, 18.23. Found: C, 52.25; H, 5.74; N, 16.30. MS (ES^+) 615.

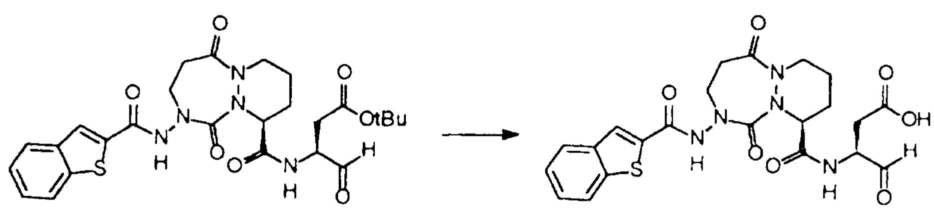
[3*S*(4*S*)] 3-[7-(Benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1053), was prepared by a similar method as used for **214** to afford a white solid (106mg, 73%): $[\alpha]_D^{20}$ +22° (c 0.10, MeOH); IR (KBr) 3428, 2944, 1733, 1652, 1532, 1433, 1337, 1288, 1186; ^1H NMR (CD_3OD) δ 7.95 (1H, s), 7.90-7.85 (2H, m), 7.43-7.35 (2H, m), 4.98 (1H, m), 4.65-4.52 (1H, m), 4.40-4.20 (2H, m), 3.85-3.70 (3H, m), 3.30-3.25 (3H, m), 3.03-2.85 (1H, m), 2.70-2.31 (3H, m), 2.10-1.55 (4H, m). MS (ES^+) 500 (as methyl acetal of the aldehyde).



528

[4*S*(2*RS*,3*S*)] 6,10-Dioxo-N-(2-ethoxy-5-oxotetrahydrofuran-3-yl)-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (528), was prepared by a similar method as compound **213e** to afford a mixture of diastereomers (Syn: anti isomer ratio 1:1) as a creamy white foamy solid (1.05g,

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1015), was prepared by a similar method as used for **265** to afford a white solid (142mg, 58%): mp. 170-5°C; $[\alpha]_D^{25}$ +32.7° (c 0.1, CH_3OH); IR (KBr) 3700-2500 (br), 3325, 2969, 1784, 1662, 1485, 1440, 1292, 1258, 1037; ^1H NMR (CD_3OD) δ 7.45 (1H, dd), 7.32 (1H, d), 6.90 (1H, d), 6.05 (2H, s), 5.10-4.90 (1H, m), 4.62-4.54 (1H, m), 4.45-4.35 (1H, m), 4.33-4.22 (1H, m), 3.95-3.65 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.20-1.50 (4H, m).



526 **1053**

[3*S*(4*S*)] t-Butyl 3-[7-(benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine]-4-oxobutanoate semicarbazone (526), was prepared by a similar method as used for **502** to afford a glassy solid: $[\alpha]_D^{20}$ +34° (c 0.13, CH_2Cl_2); IR (KBr) 3437, 2929, 1670, 1530, 1428, 1288, 1156; ^1H NMR ($CDCl_3$) δ 10.0 (1H, bs), 9.74 (1H, bs), 7.93 (1H, s), 7.80-7.60 (2H, m), 7.40-7.18 (3H, m), 6.15-5.30 (2H, bs), 5.00-4.85 (2H, m), 4.50-4.25 (1H, m), 3.95-3.75 (3H, m), 3.12-2.78 (2H, m), 2.73-1.60 (7H, m), 1.36 (9H, s). Anal. Calcd for

(0.194g, 100%): mp. 138-142°C; $[\alpha]_D^{20}$ +36.3° (c 0.19, CH_3OH); IR (KBr) 3434-2962, 1782, 1660, 1607, 1537, 1504, 1441, 1424, 1313, 1293, 1258, 1177; ^1H NMR (CD_3OD) δ 7.11 (2H, d, J = 8.8), 6.90 (2H, d, J = 8.9), 4.48 (1H, m), 4.34, 4.28 (1H, 2m), 4.15 (1H, m), 3.75 (3H, s), 3.75, 3.70 (3H, m), 2.88, 2.49, 2.28, 2.23, 2.00, 1.86, 1.79, 1.58 (8H, m).

[3*S*(4*S*)] 3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (1027), was synthesized by a similar method as compound **265** to afford a white foam (88%): $[\alpha]_D^{24}$ +22.6° (c 0.17, MeOH); IR (KBr) 3349, 1789, 1663, 1537, 1448, 1337, 1169, 1092, 690; ^1H NMR (CD_3OD) δ 7.82 (2H, d, J = 7.8), 7.57 (3H, m), 4.74 (1H, m), 4.47 (1H, m), 4.24-4.10 (2H, m), 3.72-3.47 (4H, m), 2.62-2.48 (3H, m), 2.20 (1H, m), 1.94-1.35 (3H, m). MS (ES^+) 480 (M^+ - 1, 100%). Accurate mass calculated for $C_{19}H_{24}SN_5O_8$ (MH^+): 482.1346. Found: 482.1325.

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(4-hydroxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1056), was prepared by the method used for **265** (95%): mp. >300°C; IR (KBr) 3392, 1660, 1610, 1507, 1442, 1280, 1171, 1149, 1133. ^1H NMR (CD_3OD) δ 7.74 (2H, d J = 8.7), 6.84 (2H, d J = 8.7) 4.58 (1H, m), 4.41 (1H, bd, J = 12.6), 4.28 (1H, m), 3.85 (3H, m), 2.98 (1H, m), 2.8-2.3 (3H, m), 2.3-1.6 (4H, m).

oxobutanoic acid (1075), was prepared by a similar method as compound **265** to afford a white solid (184mg, 83%): mp. 210-5°C; $[\alpha]_D^{24}$ +43.9° (c 0.1, CH_3OH); IR (KBr) 3700-2300 (br), 3309, 1660, 1537, 1423, 1311, 1262, 1184; ^1H NMR (CD_3OD) δ 7.61 (1H, d), 7.45 (1H, d), 7.28-7.15 (1H, m), 7.15-7.00 (1H, m), 7.13 (1H, s), 5.12-4.96 (1H, m), 4.62-4.55 (1H, m), 4.50-4.25 (2H, m), 4.00-3.69 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.25-1.50 (4H, m). MS (ES^+) 484 (M+, 26%), 483 (M^+ - 1, 100), 383 (25), 245 (12), 208 (11), 200 (21), 174 (31), 137 (18).

[3*S*(4*S*)] 3-{7-[(4-Acetamido)benzamido]-6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxamido}-4-oxobutanoic acid (1018), was prepared by a similar method as compound **265** to afford a white solid (177mg, 82%): mp. 235-40°C; $[\alpha]_D^{23}$ +27.3° (c 0.1, CH_3OH); IR (KBr) 3700-2300 (br), 3311, 2957, 1662, 1599, 1531, 1318, 1266, 1182; ^1H NMR (CD_3OD) δ 7.83 (2H, d), 7.69 (2H, d), 5.10-4.95 (1H, m), 4.64-4.55 (1H, m), 4.50-4.35 (1H, m), 4.32-4.22 (1H, m), 4.00-3.65 (3H, m), 3.05-2.90 (1H, m), 2.80-2.30 (3H, m), 2.15 (3H, s), 2.15-1.50 (4H, m). Anal. Calcd for $C_{22}H_{26}N_6O_8 \cdot 1.5H_2O$: C, 49.90; H, 5.52; N, 15.87. Found: C, 50.21; H, 5.41; N, 15.49. MS (ES^+) 502 (M+, 28%), 501 (M^+ - 1, 100), 401 (8), 218 (4), 119 (2), 118 (5), 113 (16).

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (1052), was synthesized via method used to prepare **265** to afford a white solid

[3*S*(4*S*)] 3-(6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido)-4-oxobutanoic acid (1095), was prepared by a similar method as compound **265** to afford a white solid (84mg, 90%): mp. 180-6°C; $[\alpha]_D^{22}$ +22.3° (c 0.065, CH_3OH); IR (KBr) 3700-2300 (br), 3287, 1664, 1536, 1425, 1261, 1181; ^{1}H NMR (CD_3OD) δ 7.35-7.20 (5H, m), 5.00-4.90 (1H, m), 4.60-4.50 (1H, m), 4.50-4.10 (2H, m), 3.90-3.50 (3H, m), 3.54 (2H, s), 3.00-2.80 (1H, m), 2.80-2.40 (2H, m), 2.35-2.20 (1H, m), 2.20-1.50 (4H, m). MS (ES^+) 459 (M+ 24%), 458 (M^+ - 1, 100), 358 (27), 175 (9), 149 (7), 137 (12). Accurate mass calculated for $C_{21}H_{26}N_5O_7$ (MH^+): 460.1832. found: 460.1840.

[3*S*(4*S*)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265f), was prepared by a similar method as compound **265** to afford a white foamy solid (130mg, 88%): mp. 157-62°C; $[\alpha]_D^{24}$ +41.7° (c 0.1, CH_3OH); IR (KBr) 3700-2300 (br), 3325, 1782, 1663, 1547, 1443, 1315, 1242, 1181; ^{1}H NMR (CD_3OD) δ 7.40 (2H, dd), 7.35-7.20 (2H, m), 7.06-6.95 (1H, m), 5.05-4.95 (1H, m), 4.64-4.54 (1H, m), 4.50-4.35 (1H, m), 4.35-4.15 (1H, m), 3.90-3.69 (3H, m), 3.00-2.85 (1H, m), 2.80-2.45 (3H, m), 3.40-1.50 (4H, m). MS (ES^+) 460 (M+, 24%), 459 (M^+ - 1, 100), 341 (9), 340 (54), 296 (6), 239 (9).

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-

17%): mp. 126-30°C (dec); $[\alpha]_D^{20}$ +30° (c 0.05, MeOH); IR (KBr) 3371, 2935, 1785, 1663, 1538, 1418, 1339, 1164, 669; ^{1}H NMR (CD_3OD) δ 8.44 (1H, s), 8.06-7.50 (7H, m), 7.22 (1H, d, J = 8.4), 4.58-4.57 (1H, m), 4.46-4.42 (1H, m), 4.16-4.09 (2H, m), 3.85-3.50 (3H, m), 2.84-2.78 (1H, m), 2.64-2.51 (1H, m), 2.44-2.15 (2H, m), 1.81-0.89 (4H, m). Anal. Calcd for $C_{23}H_{25}N_5O_8S\cdot H_2O$: C, 50.27; H, 4.95; N, 12.74. Found: C, 50.33; H, 5.04; N, 12.60. MS (ES^+) 530.

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265c), was prepared by a similar method as **265**, (90%) as a colourless solid: mp. ~150°C (decomp.); $[\alpha]_D^{23}$ +94.8° (c 0.1, 20% MeOH/CH_2Cl_2); IR (KBr) 3330, 1780, 1660, 1610, 1550, 1495, 1428, 1326, 1287, 1251, 1223, 1160; ^{1}H NMR (CD_3OD) δ 7.16 (2H, m), 6.89 (1H, d, J = 7.8), 4.58 (1H, m), 4.37 (2H, m), 3.76 (6H, s + m), 2.95 (1H, m), 2.67 (1H, m), 2.33 (1H, m), 2.20-1.85 (3H, m), 1.66 (1H, m).

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxamido]-4-oxobutanoic acid (265d), was prepared by a similar method as **265**, (85%) as a colourless solid: mp. ~176-85°C; $[\alpha]_D^{23}$ +11.0° (c 0.1, MeOH); IR (KBr) 3392, 3328, 1784w, 1665, 1603, 1537, 1490, 1462, 1437, 1337, 1290, 1290, 1217, 1177, 1119, 1023; ^{1}H NMR (CD_3OD) δ 8.02 (2H, m), 6.95 (4H, m), 5.05 (1H, m), 4.60 (2H, m), 3.92 (4H, s + m), 3.00 (2H, m), 2.68 (1H, m), 2.39 (1H, m), 2.00 (4H, m), 1.69 (1H, m).

(264k), was prepared by the method used for **213e** (96%): IR (KBr) 3294, 2946, 1793, 1658, 1606, 1535, 1501, 1248, 1174, 1119. ^1H NMR ($CDCl_3$) δ 8.91 (1H, s), 7.85 (3H, m), 7.4 (10H, m), 7.02 (2H, d), 5.35 (1H, s), 5.10 (2H, s), 4.8-4.3 (5H, m), 4.00 (1H, bs), 3.78 (2H, m), 2.90 (2H, m), 2.5-1.5 (6H, m).

[4*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264l), was prepared by a similar method as compound **213e** to afford a mixture of diastereomers (syn:anti isomer ratio 1:1) as a white solid (1.72g, 71%): mp. 148-60°C; IR (KBr) 3314, 1780, 1677, 1658, 1651, 1550, 1485, 1439, 1258, 1132, 1038, 943; ^1H NMR (D_6-DMSO) δ 10.39 (1H, s), 8.71 (0.5H, d), 8.49 (0.5H, d), 7.44 (1H, d), 7.42-7.30 (6H, m), 7.03 (1H, d), 6.12 (2H, s), 5.68 (0.5H, d), 5.45 (0.5H, s), 4.90-4.82 (1H, m), 4.82-4.58 (2.5H, m), 4.40-4.10 (1.5H, m), 3.90-3.65 (2H, m), 3.65-3.43 (1H, m), 3.09 (0.5H, dd), 2.90-2.55 (1.5H, m), 2.45-2.10 (2H, m), 2.10-1.35 (4H, m). Anal. Calcd for $C_{28}H_{29}N_5O_9 \cdot 0.2H_2O$: C, 57.67; H, 5.08; N, 12.01. Found: C, 58.01; H, 5.33; N, 11.51. MS (ES^+) 581 (M^+ + 2, 33%), 580 (M+, 100), 374 (9), 373 (48), 345 (12), 261 (4), 239 (7), 149 (9).

[3*S*(4*S*)] 3-[6,10-Dioxo-7-(2-naphthalenesulfonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamido]-4-oxobutanoic acid (265a), was prepared by a similar method as compound **265** to afford a white solid (37mg,

(264i), was prepared by a similar method to that described for compound **213e** to afford a white solid (70%): mp. 116-118°C; IR (KBr) 3315, 2951, 1793, 1664, 1607, 1502, 1258, 1177; ^{1}H NMR ($CDCl_3$) δ 8.07 (1H, s), 7.77 (2H, d, J = 8.6), 7.35 (5H, m), 6.94 (2H, d, J = 8.5), 6.74 (1H), 4.89 (1H, d, J = 11.1), 4.74 (1H, m), 4.60 (1H, d, J = 11.0), 4.48, 4.41 (1H, 2m), 3.86 (3H, s), 3.79, 3.71-3.53 (3H, 2m), 2.87 (2H, m), 2.44 (1H, m), 2.18, 1.91, 1.68 (5H, 3m).

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl) 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264j), was synthesized by a similar method as compound **213e** to afford a foam (88%): $[\alpha]_D^{24}$ +74.2° (c 0.36, CH_2Cl_2); IR (KBr) 3332, 3235, 1793, 1664, 1537, 1448, 1416, 1337, 1169, 118, 1092, 940, 690; ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, s), 7.88 (2H, d, J = 6.8), 7.64-7.48 (3H, m), 7.34 (5H, s), 7.13 (1H, d, J = 6.9), 5.39 (1H, s), 4.81 (2H, m), 4.62 (1H, d, J = 11.5), 4.48 (1H, m), 4.33 (1H, m), 3.85 (1H, m), 3.59 (2H, m), 3.03 (1H, dd, J = 7.6, 18.2), 2.49-2.28 (3H, m), 1.94-1.40 (4H, m). Anal. Calcd for $C_{26}H_{29}SN_5O_8$: C, 54.63; H, 5.11 N, 12.25. Found: C, 54.42; H,5.28; N, 11.62. MS (ES^+) 572 (MH^+, 100%). Accurate mass calculated for $C_{26}H_{30}SN_5O_8$ (MH^+): 572.1815. Found: 572.1802.

[4*S*(2*RS*,3*S*)] 7-(4-Benzyloxyphenyl)carbonylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide

CH_2Cl_2); IR (KBr) 3404, 3295, 1789, 1660, 1536, 1421, 1310, 1260, 1122, 749; ^1H NMR (D_6-DMSO) δ 11.72 (1H, s), 10.58 (1H, s), 8.73 (1H, d), 7.65 (1H, d), 7.58-7.27 (6H, m), 7.27-7.10 (1H, m), 7.17 (1H, s), 7.10-7.00 (1H, m), 5.46 (1H, s), 4.90-4.85 (1H, m), 4.77 and 4.68 (2H, dd), 4.35-4.25 (2H, m), 3.95-3.55 (3H, m), 3.09 (1H, dd), 2.95-2.80 (1H, m), 2.47-2.25 (2H, m), 2.10-1.35 (4H, m). MS (ES^+) 574 (M+, 35%), 573 (M^+ - 1, 100), 384 (16), 383 (69), 341 (23), 327 (12), 267 (13), 200 (22).

[4*S*(2*RS*,3*S*)] 7-[(4-Acetamido)benzamido]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264h), was prepared by a similar method as compound **213e** to afford a mixture of diastereomers (Syn:anti isomer ratio 9:1) as a white solid (276mg, 70%): mp. 147-52°C; IR (KBr) 3444, 3304, 1793, 1665, 1602, 1531, 1505, 1423, 1294, 1264, 1181, 1123, 966; ^1H NMR (D_6-DMSO) δ 10.41 (1H, s), 10.22 (1H, s), 8.71 (0.1H, d), 8.48 (0.9H, d), 7.78 (2H, d), 7.67 (2H, d), 7.35-7.30 (5H, m), 5.68 (0.9H, d), 5.45 (0.1H, s), 4.88-4.80 (1H, m), 4.75-4.60 (1H, m), 4.77 and 4.63 (2H, dd), 4.30-4.20 (1H, m), 3.90-3.50 (3H, m), 3.10-2.50 (3H, m), 2.35-2.20 (1H, m), 2.07 (3H, s), 2.05-1.35 (4H, m). Anal. Calcd for $C_{29}H_{32}N_6O_8 \cdot 1H_2O$: C, 57.04; H, 5.61; N, 13.76. Found: C, 56.79; H, 5.50; N, 13.53. MS (ES^+) 594 (M^+ + 2, 34%), 593 (M^+ + 1, 100), 387 (8), 386 (38), 358 (8), 162 (19).

[4*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide

4.85-4.75 (1H, m), 4.74-4.60 (1H, m), 4.77 and 4.63 (2H, dd), 4.30-4.10 (1H, m), 3.80-3.40 (3H, m), 3.43 (2H, s), 3.10-2.40 (3H, m), 2.25-2.15 (1H, m), 2.00-1.35 (4H, m). Anal. Calcd for $C_{28}H_{31}N_5O_7 \cdot 0.5H_2O$: C, 60.21; H, 5.77; N, 12.53. Found: C, 60.38; H, 5.83; N, 12.13. MS (ES^+) 551 (M^+ + 2, 33%), 550 (M^+ + 1, 100), 480 (7), 343 (8), 279 (4).

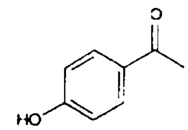
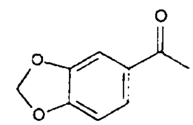
[4*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264f), was prepared by a similar method as compound **213e** to afford the pure syn-isomer as a white foamy solid (225mg, 82%): mp. 130-5°C; $[\alpha]_D^{24}$ +10.8° (c 0.1, CH_2Cl_2); IR (KBr) 3316, 1791, 1688, 1676, 1664, 1601, 1536, 1445, 1314, 1242, 973; ^1H NMR (D_6-DMSO) δ 8.84 (1H, s), 8.49 (1H, d), 8.19 (1H, s), 7.45-7.18 (9H, m), 7.00-6.90 (1H, m), 5.68 (1H, d), 4.90-4.81 (1H, m), 4.75-4.60 (1H, m), 4.78 and 4.63 (2H, dd), 4.30-4.20 (1H, m), 3.75-3.55 (3H, m), 2.85-2.55 (3H, m), 2.25-2.15 (1H, m), 2.00-1.35 (4H, m). Anal. Calcd for $C_{27}H_{30}N_6O_7 \cdot 0.5H_2O$: C, 57.95; H, 5.58; N, 15.02. Found: C, 58.12; H, 5.64; N, 14.81. MS (ES^+) 552 (M^+ + 2, 30%), 551 (M^+ + 1, 100), 362 (19), 299 (10), 279 (4).

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264g), was prepared by a similar method as compound **213e** to afford the pure anti-isomer as a white solid (284mg, 80%): mp. 148-53°C; $[\alpha]_D^{24}$ +72.0° (c 0.1,

1608, 1543, 1496, 1455, 1428, 1325, 1287, 1250, 1218, 1160, 1118; ^1H NMR ($CDCl_3$) δ 8.00 (1H, d, J = 7.1), 7.66 (1H, s), 7.55 (1H, s), 7.28 (5H, m), 7.14 (2H, m), 6.87 (1H, d, J = 7.4), 6.59 (1H, m), 5.42 (1H, s), 4.66 (5H, m), 3.90-3.65 (4H, m), 3.73 (3H, s), 2.98 (2H, m), 2.38 (2H, m), 2.01-1.65 (3H, m).

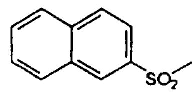
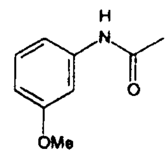
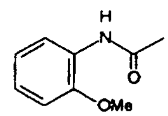
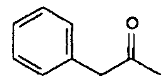
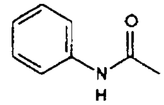
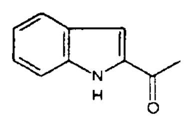
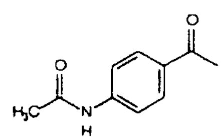
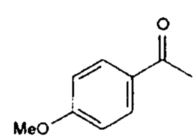
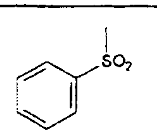
[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-1-carboxamide (264d), was prepared by a similar method as **213e**, (72%) as colourless foam: $[\alpha]_D^{22}$ +21.4° (c 0.1, CH_2Cl_2); IR (KBr) 3302, 1791, 1689, 1678, 1664, 1602, 1536, 1489, 1461, 1437, 1420, 1249, 1119, 1023, 942, 751; ^1H NMR ($CDCl_3$) δ 8.07 (1H, d, J = 7.7), 7.82 (1H, s), 7.68 (1H, d, J = 6.7), 7.49 (1H, s), 7.34 (5H, m), 6.96 (3H, m), 5.47 (1H, s), 4.82 (2H, d + m, J = 11.5), 4.63 (1H, d, J = 11.5), 4.49 (2H, m), 3.85 (4H, s + m), 3.68 (2H, m), 3.01 (2H, m), 2.46 (2H, m), 1.95 (3H, m), 1.57 (1H, m).

[4*S*(2*RS*,3*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264e) was synthesized via a similar method as used to prepare **213e** to afford a mixture of diastereomers (Syn:anti isomer ratio 9:1) as a white glassy solid (128mg, 78%): mp. 103-8°C; IR (KBr) 3419, 3302, 1793, 1664, 1535, 1421, 1327, 1256, 1123, 973; ^1H NMR (D_6-DMSO) δ 10.20 (0.9H, s), 9.35 (0.1H, s), 8.74 (0.1H, d), 8.49 (0.9H, d), 7.36-7.15 (10H, m), 5.67 (0.9H, d), 5.44 (0.1H, s),

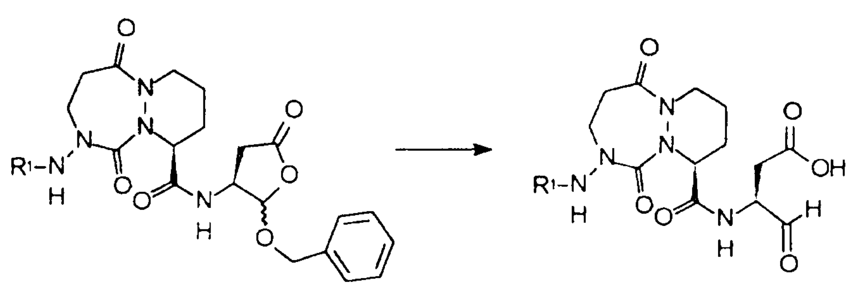
264k **1056**	
2641 **1015**	

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-7-(2-naphthalenesulfonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxamide (264a), was synthesized by a similar method as compound **213e** to afford a white solid (240mg, 82%): IR (KBr) 3380, 3066, 2947, 1789, 1750, 1691, 1454, 1417, 1368, 1298, 1262, 1235, 1193, 1118, 756, 696; ^{1}H NMR (D_6-DMSO) δ 8.59 (1H, d, J = 6.8), 8.48 (1H, s), 8.25-8.09 (3H, m), 7.85-7.75 (3H, m), 7.36 (5H, m), 5.39 (1H, m), 4.21 (2H, AB, J = 14.2), 4.53-4.49 (1H, m), 4.25-4.10 (2H, m), 3.65-3.44 (3H, m), 3.13-2.99 (1H, m), 2.43-2.16 (1H, m), 1.72-0.72 (7H, m). Anal. Calcd for $C_{30}H_{31}N_5O_8S$: C, 57.96; H, 5.03; N, 11.27. Found: C, 57.28; H, 5.14; N, 10.48. MS (ES^+) 622.

[4*S*(2*S*,3*S*)] N-(2-Benzyloxy-5-oxo-tetrahydrofuran-3-yl)-6,10-dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-1-carboxamide (264c), was prepared by a similar method as **213e**, (55%) as a colourless foam: mp. 135-40°C; $[\alpha]_D^{22}$ +51.6° (c 0.1, CH_2Cl_2); IR (KBr) 3314, 1790, 1664,

compound	R^1
264a 265a	
264c 265c	
264d 265d	
264e 1095	
264f 265f	
264g 1075	
264h 1018	
264i 1052	
264j 1027	

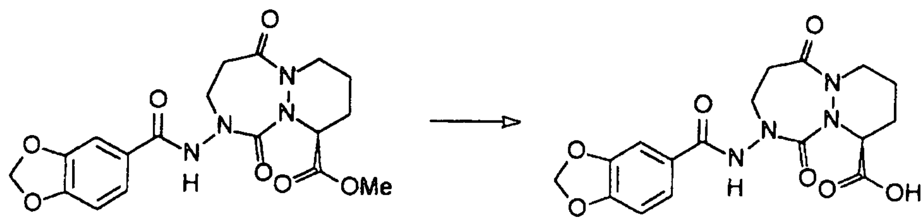
pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (2631). A suspension of **5251** (3.32g, 8.2mmol) in tetrahydrofuran (60ml) was treated with a solution of LiOH•H_2O (0.69g, 16.4mmol, 2.0 equiv) in water (20ml). The resulting mixture was stirred for 1h, concentrated and the residue dissolved in water (50ml). The solution was acidified using 2M. $NaHSO_4$ and the product extracted with EtOAc (100ml and 50ml portions). The combined extract was washed once with brine (2 x 50ml), dried ($MgSO_4$) and concentrated to afford **2631** as a white crystalline solid (2.87g, 90%): mp. 154-8°C; $[\alpha]_D^{20}$ +85.6° (c 0.01, CH_3OH); IR (KBr) 3700-2300 (br), 3248, 2942, 1733, 1681, 1658, 1648, 1536, 1486, 1440, 1297, 1255, 1037; ^1H NMR (D_6-DMSO) δ 13.23 (1H, bs), 10.45 (1H, s), 7.45 (1H, d), 7.35 (1H, s), 7.03 (1H, d), 6.12 (2H, s), 5.00-4.93 (1H, m), 4.35-4.25 (1H, m), 3.90-3.40 (3H, m), 2.95-2.70 (1H, m), 2.40-2.25 (1H, m), 2.15-2.00 (1H, m), 1.91-1.40 (3H, m). Anal. Calcd for $C_{17}H_{18}N_4O_7$•$0.8H_2O$: C, 50.45; H, 4.88; N, 13.84. Found: C, 50.80; H, 4.95; N, 13.36. MS (ES^+) 390 (M^+, 19%), 389 (M^+ - 1, 100), 345 (9), 204 (31), 182 (27), 111 (12).



264a, c-l

265a, c, d, f
1015, 1018, 1027,
1052, 1056, 1075, 1095

2945, 1738, 1650, 1611, 1501, 1445, 1309, 1255, 1171; ^1H NMR ($CDCl_3$) δ 9.35 (1H, s), 7.74 (2H, d), 7.38 (5H, m), 6.85 (2H, d), 5.40 (1H, bs), 5.19 (1H, s), 5.02 (2H, s), 4.49 (1H, d), 3.92 (2H, m), 3.68 (1H, m), 2.99 (1H, bs), 2.43 (1H, bs), 2.22 (1H, bs), 1.99 (1H, bs), 1.68 (2H, bs).



5251 2631

(4*S*) Methyl 6,10-dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (5251), was synthesized via method used to prepare **211** to afford a white crystalline solid (3.35g, 83%): mp. 214-5°C; $[\alpha]_D^{20}$ +75.2° (c 0.1, CH_2Cl_2); IR (KBr) 3272, 2955, 1747, 1664, 1610, 1485, 1443, 1265, 1040; ^1H NMR ($CDCl_3$) δ 8.66 (1H, s), 7.32 (1H, dd), 7.23 (1H, d), 6.76 (1H, d), 6.02 (2H, s), 5.20 (1H, dd), 4.55-4.45 (1H, m), 4.03-3.70 (3H, m), 3.78 (3H, s), 3.05-2.88 (1H, m), 2.47-2.35 (1H, m), 2.35-2.20 (1H, m), 2.10-1.90 (1H, m), 1.85-1.50 (2H, m). Anal. Calcd for $C_{18}H_{20}N_4O_7 \cdot 0.5H_2O$: C, 52.87; H, 5.06; N, 13.70. Found: C, 52.84; H, 5.00; N, 13.66. MS (ES^+) 406 (M^+ + 2, 20%), 405 (M^+ + 1, 100), 391 (10), 162 (6), 148 (3), 105 (2).

(4*S*) 6,10-Dioxo-7-(3,4-methylenedioxybenzoylamino)-1,2,3,4,7,8,9,10-octahydro-6H-

(M+, 10%), 402 (M^+ - 1, 100), 358 (10), 247 (10), 227 (16), 219 (51), 198 (12), 184 (17).

(4*S*) 6,10-Dioxo—7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-carboxylic acid (263i), was obtained as a white glassy solid (approx 100%) used without purification: ^{1}H NMR ($CDCl_3$) δ 9.23 (1H, s), 7.72 (2H, d, J = 8.8), 6.81 (2H, d, J = 8.9), 5.22 (1H, m), 4.51 (1H, m), 3.97-3.72 (2H, m), 3.81 (3H, s), 3.03 (1H, m), 2.51-2.46 (1H, m), 2.31-2.25 (1H, m), 2.03 (1H, m), 1.72 (2H, m).

(4*S*) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263j), was obtained as a white solid (100%): mp. 73-83°C (dec); $[\alpha]_D^{22}$ +104.7° (c 0.3, CH_2Cl_2); IR (KBr) 3600-2500 (br), 3208, 1734, 1666, 1481, 1448, 1416, 1338, 1311, 1214, 1171, 1091, 729, 689; ^{1}H NMR ($CDCl_3$) δ 7.87 (3H, m), 7.70-7.50 (3H, m), 7.16 (1H, brs), 4.99 (1H, m), 4.37 (1H, brd, J = 12.8), 3.92 (1H, m), 3.67 (2H, m), 2.36 (2H, m), 2.13 (1H, brd, J = 12.2), 1.56 (3H, m). Anal. Calcd for $C_{15}H_{18}SN_4O_6 \cdot 0.25CF_3CO_2H$: C, 45.31; H, 4.48 N, 13.64. Found: C, 45.48; H, 4.71; N, 13.43. MS (ES^+) 383 (MH^+, 100%). Accurate mass calculated for $C_{15}H_{19}SN_4O_6$ (MH^+): 383.1025. Found: 383.1007.

(4*S*) 7-(4-Benzyloxyphenyl)carbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263k), (100%) obtained: mp. 130-142°C; IR (KBr) 3272,

18.42. MS (ES^+) 361 (M+, 20%), 360 (M^+ - 1, 100), 241 (11), 240 (89), 196 (15), 175 (29), 111 (12).

(4*S*) 6,10-Dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263g), was obtained as a white solid (259mg, 92%)mp. 248-51°C; $[\alpha]_D^{24}$ +94.0° (c 0.01, CH_3OH); IR (KBr) 3700-2300 (br) 3341, 2956, 1738, 1668, 1651, 1529, 1425, 1311, 1259, 751; ^1H NMR (D_6-DMSO) δ 13.29 (1H, bs), 11.72 (1H, s), 10.64 (1H, s), 7.65 (1H, d), 7.45 (1H, d), 7.26-7.15 (1H, m), 7.17 (1H, s), 7.10-7.00 (1H, m), 5.05-4.95 (1H, m), 4.40-4.25 (1H, m), 3.90-3.50 (3H, m), 2.88-2.75 (1H, m), 2.38-2.20 (1H, m), 2.20-2.00 (1H, m), 1.90-1.35 (3H). Anal. Calcd for $C_{18}H_{19}N_5O_5 \cdot 0.5H_2O$: C, 53.59; H, 5.25; N, 17.35. Found: C, 53.66; H, 4.88; N, 17.11. MS (ES^+) 385 (M+, 23%), 384 (M^+ - 1, 100), 298 (6), 253 (8), 227 (10), 199 (23), 196 (10), 173 (9), 126 (21).

(4*S*) 7-[(4-Acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263h), was obtained as a white solid (282mg, 99%): mp. 210-5°C; $[\alpha]_D^{24}$ +74.5° (c 0.01, CH_3OH); IR (KBr) 3700-2300 (br) 3444, 3316, 2960, 1664, 1599, 1531, 1439, 1301, 1184; ^1H NMR (D_6-DMSO) δ 13.30 (1H, bs), 10.50 (1H, s), 10.25 (1H, s), 7.80 (2H, d), 7.68 (2H, d), 5.00-4.90 (1H, m), 4.35-4.25 (1H, m), 3.90-3.40 (3H, m), 2.88-2.70 (1H, m), 2.35-2.25 (1H, m), 2.25-1.95 (1H, m), 2.08 (3H, s), 1.95-1.35 (3H, m). MS (ES^+) 403

m), 7.97 (2H, m), 7.15-6.84 (3H, m), 5.29 (1H, m), 4.62 (1H, m), 4.04-3.65 (4H, m), 3.89 (3H, s), 2.92 (1H, m), 2.50 (1H, m), 2.30 (1H, m), 2.10-1.75 (2H, m).

(4*S*) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetyl-amino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263e), obtained as a white foamy solid (117mg, 98%): mp. 109-14°C; $[\alpha]_D^{24}$ +82.6° (c 0.06, CH_2Cl_2); IR (KBr) 3700-2250 (br), 3437, 3274, 2959, 1733, 1664, 1481, 1437, 1310, 1177; ^1H NMR ($CDCl_3$) δ 7.99 (1H, s), 7.40-7.15 (5H, m), 5.15-5.10 (1H, m), 5.25-4.70 (1H, bs), 4.50-4.35 (1H, m), 3.95-3.50 (3H, m), 3.61 (2H, s), 2.93-2.78 (1H, m), 2.40-2.20 (2H, m), 2.10-1.80 (1H, m), 1.80-1.60 (2H, m). Anal. Calcd for $C_{17}H_{20}N_4O_5 \cdot 1H_2O$: C, 53.96; H, 5.86; N, 14.81. Found: C, 54.12; H, 5.50; N, 14.68. MS (ES^+) 360 (M+, 21%), 359 (M^+ - 1, 100), 196 (14), 182 (14), 111 (7).

(4*S*) 6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263f), obtained as a white foamy solid (199mg, 92%): mp. 149-52°C; $[\alpha]_D^{24}$ +92.0° (c 0.01, CH_3OH); IR (KBr) 3700-2300 (br), 3319, 2956, 1726, 1664, 1600, 1548, 1500, 1444, 1313, 1238, 755; ^1H NMR (D_6-DMSO) δ 8.90 (1H, s), 8.24 (1H, s), 7.42 (2H, d), 7.30-7.20 (2H, m), 7.00-6.90 (1H, m), 4.98-4.92 (1H, m), 4.32-4.22 (1H, m), 3.80-3.55 (3H, m), 2.85-2.70 (1H, m), 2.30-2.20 (1H, m), 2.20-2.00 (1H, m), 1.90-1.35 (3H, m). Anal. Calcd for $C_{16}H_{19}N_5O_5 \cdot 0.75H_2O$: C, 51.26; H, 5.51; N, 18.68. Found: C, 51.11; H, 5.23; N,

2.01 (1H, m), 1.91-1.83 (1H, m), 1.46-1.26 (1H, m), 1.13-1.06 (1H, m), 0.90-0.77 (1H, m). MS (ES^+) 431.

(4*S*) 7-(Benzo[b]thiophene-2-carbonyl)amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263b). 200mg (100%) was obtained as a white solid: mp. 155°C; $[\alpha]_D^{20}$ +13° (c 0.07, CH_2Cl_2); IR (KBr) 3431, 2935, 1734, 1663, 1531, 1435, 1292, 1177; ^1H NMR ($CDCl_3$) δ 9.73 (1H, bs), 7.73-7.27 (5H, m), 5.35-5.25 (1H, m), 4.56-4.48 (1H, m), 4.05-3.65 (3H, m), 3.12-3.00 (1H, m), 2.50-2.45 (1H, m), 2.30-2.20 (1H, m), 2.10-2.00 (1H, m), 1.75-1.61 (2H, m). MS (ES^+) 401.

(4*S*) 6,10-Dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263c), 216mg, (100+%) obtained as a colourless foam: $[\alpha]_D^{23}$ 32.5° (c 0.1, CH_2Cl_2); IR (KBr) 3326, 1730, 1661, 1610, 1555, 1495, 1431, 1314, 1288, 1217, 1175, 1161; ^1H NMR ($CDCl_3$) δ 7.87 (1H, s), 7.58 (1H, s), 7.19 (2H, m), 6.82 (1H, m), 6.62 (1H, m), 5.21 (1H, m), 4.55 (1H, m), 3.76 (3H, s), 4.0-3.65 (4H, m), 2.85 (1H, m), 2.35 (2H, m), 1.75 (1H, m), 1.71 (2H, m).

(4*S*) 6,10-Dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263d), (100+%) obtained as colourless foam: $[\alpha]_D^{24}$ +11.7° (c 0.1, CH_2Cl_2); IR (KBr) 3394, 3325, 1666, 1603, 1543, 1490, 1463, 1438, 1329, 1311, 1292, 1249, 1214, 1176, 1119, 1024, 752; ^1H NMR ($CDCl_3$) δ 8.15 (1H,

IR (KBr) 3283, 1732, 1684, 1448, 1430, 1404, 1369, 1338, 1306, 1285, 1242, 1169, 1091, 692; ^1H NMR ($CDCl_3$) δ 7.89 (2H, d, J = 7.4), 7.76 (1H, s), 7.64-7.49 (3H, m), 4.83 (1H, m), 4.35 (1H, brd, J = 13.0), 4.00 (1H, m), 3.74-3.63 (2H, m), 2.39-2.26 (2H, m), 2.06 (1H, m), 1.50-1.41 (10H, m). Anal. Calcd for $C_{19}H_{26}SN_4O_6$: C, 52.04; H, 5.98 N, 12.78. Found: C, 52.11; H, 5.95; N, 12.71. MS (ES^+) 437 (M^+ - 1, 100%).

(3*S*) t-Butyl (7-(4-benzyloxyphenyl)carbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262k), (83%) was obtained: $[\alpha]_D^{22}$ +42.3°. (c 0.11, CH_2Cl_2);.IR (KBr) 3287, 2997, 2935, 1735, 1681, 1606, 1501, 1296, 1248, 1173,1155. ^1H NMR ($CDCl_3$) δ 9.23 (1H, s), 7.73 (2H, d), 7.38 (5H, m), 6.85 (2H, d), 5.08 (1H, m), 5.02 (2H, s), 4.48 (1H, bd), 4.15-3.65 (3H, m), 2.96 (1H, m), 2.45-2.10 (2H, m), 1.88 (1H, m), 1.63 (2H, m), 1.48 (9H, s). M.S. (ES^+ 509 (M^++1).

Compounds **263a-k** were synthesized via methods used to prepare **212b-f**.

(4*S*) 6,10-Dioxo-7-(2-naphthalenesulfonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylic acid (263a), 348mg (94%) obtained as a white foamy solid: mp. $[\alpha]_D^{21}$ +171° (c 0.056, CH_2Cl_2); IR (KBr) 3426, 3233, 2953, 1734, 1663, 1481, 1415, 1340, 1214, 1167, 1132, 1075, 668; ^1H NMR ($CDCl_3$) δ 8.44 (1H, s), 8.00-7.60 (7H, m), 4.85-4.83 (1H, m), 4.25-4.00 (1H, m), 4.07-3.90 (1H, m), 3.70-3.46 (2H, m), 2.38-2.30 (1H, m), 2.12-

(4*S*) t-Butyl 7-[(4-acetamido)benzamido]-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]-triazepine-4-carboxylate (262h), was obtained as a white solid (325mg, 73%): mp. 209-12°C; $[\alpha]_D^{24}$ +62.4° (c 0.2, CH_2Cl_2); IR (KBr) 3513, 3269, 2980, 1731, 1680, 1653, 1599, 1531, 1314, 1158; ^1H NMR ($CDCl_3$) δ 9.40 (1H, s), 8.75 (1H, s), 7.72 (2H, d), 7.47 (2H, d), 5.15-5.05 (1H, m), 4.55-4.45 (1H, m), 4.05-3.70 (3H, m), 3.00-2.80 (1H, m), 2.45-2.35 (1H, m), 2.30-2.15 (1H, m), 2.10 (3H, s), 2.00-1.80 (1H, m), 1.80-1.50 (2H, m), 1.48 (9H, s). Anal. Calcd for $C_{22}H_{29}N_5O_6$: C, 57.51; H, 6.36; N, 15.24. Found: C, 57.41; H, 6.38; N, 15.12. MS (ES^+) 461 (M^+ + 2, 26%), 460 (M^+ + 1, 100), 405 (12), 404 (55), 354 (7), 285 (23), 229 (52), 183 (22).

(4*S*) t-Butyl 6,10-dioxo-7-(4-methoxybenzoylamino)-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-carboxylate (262i), was obtained as a white glassy solid (76%): mp. 85-9°C; $[\alpha]_D^{25}$ +66.4° (c 0.11, CH_2Cl_2); IR (KBr) 1732, 1668, 1607, 1502, 1440, 1312, 1295, 1258, 1176, 1157, 1025; ^1H NMR ($CDCl_3$) δ 8.25 (1H, s), 7.77 (2H, m), 6.90 (2H, m), 5.11-5.07 (1H, m), 4.55-4.48 (1H, m), 4.01-3.91 (2H, m), 3.86-3.78 (1H, m), 3.85 (3H, s), 2.98 (1H, m), 2.46-2.40 (1H, m), 2.26-2.20 (1H, m), 2.05-1.80 (1H, m), 1.70-1.64 (2H, m), 1.48 (9H, s).

(4*S*) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylsulphonylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262j), was obtained as a white crystalline solid (79%): mp. 182-3°C (dec); $[\alpha]_D^{22}$ +92.1° (c 0.4, CH_2Cl_2);

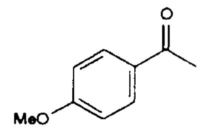
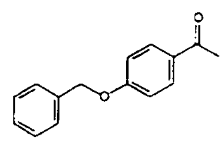
(4*S*) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-(3-phenylureido)-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262f), was obtained as a white solid (273mg, 93%): mp. 102-6°C; $[\alpha]_D^{22}$ +7.5° (c 0.07, CH_2Cl_2); IR (KBr) 3320, 2979, 1731, 1676, 1669, 1601, 1549, 1444, 1314, 1240, 1156; ^{1}H NMR ($CDCl_3$) δ 7.37-7.20 (6H, m), 7.08-6.98 (1H, m), 5.12 (1H, dd), 4.64-4.55 (1H, m), 4.02-3.78 (2H, m), 3.75-3.65 (1H, m), 2.94-2.75 (1H, m), 2.57-2.35 (1H, m), 2.35-2.20 (1H, m), 2.00-1.50 (3H, m), 1.48 (9H, s). Anal. Calcd for $C_{20}H_{27}N_5O_5$•$0.4H_2O$: C, 56.56; H, 6.60; N, 16.49. Found: C, 56.89; H, 6.58; N, 16.07. MS (ES^+) 419 (M^+ + 2, 24%), 418 (M^+ + 1, 100), 363 (15), 362 (81), 242 (10).

(4*S*) t-Butyl 6,10-dioxo-7-(indole-2-carboxamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262g), (13g) was obtained as a white solid (298mg, 70%): mp. 138-43°C; $[\alpha]_D^{23}$ +69.8° (c 0.1, CH_2Cl_2); IR (KBr) 3282, 2978, 1733, 1664, 1536, 1421, 1310, 1156, 748; ^{1}H NMR ($CDCl_3$) δ 9.67 (1H, s), 9.53 (1H, s), 7.50 (1H, d), 7.30-7.15 (2H, m), 7.10-7.00 (1H, m), 6.93 (1H, s), 5.16-5.12 (1H, m), 4.60-4.50 (1H, m), 4.05-3.85 (2H, m), 3.85-3.70 (1H, m), 3.05-2.90 (1H, m), 2.55-2.35 (1H, m), 2.35-2.20 (1H, m), 2.00-1.85 (1H, m), 1.85-1.50 (2H, m), 1.47 (9H, s). Anal. Calcd for $C_{22}H_{27}N_5O_5$•$0.45H_2O$: C, 58.77; H, 6.26; N, 15.58. Found: C, 59.14; H, 6.24; N, 15.18. MS (ES^+) 433 (M^+ + 2, 26%), 442 (M^+ + 1, 100), 387 (17), 386 (79), 285 (20), 229 (85), 211 (26), 185 (15), 183 (57), 139 (9).

$[\alpha]_D^{22}$ +22.6° (c 0.1, CH_2Cl_2); IR (KBr) 3316, 1732, 1671, 1609, 1551, 1495, 1455, 1432, 1316, 1288, 1245, 1218, 1158, 1122, 1023; ^1H NMR ($CDCl_3$) δ 7.16 (4H, m), 6.79 (1H, m) 6.60 (1H, m), 5.11 (1H, m), 4.59 (1H, m), 3.89 (2H, m), 3.77 (3H, s), 3.72 (2H, m), 2.85 (1H, m).

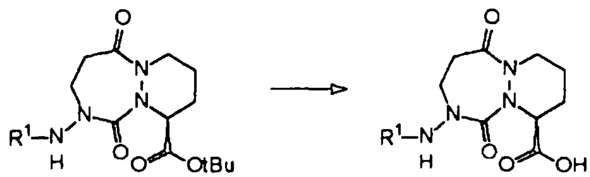
(4*S*) t-Butyl 6,10-dioxo-7-(2-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino [1,2-a][1,2,4]triazepine-4-carboxylate (262d), (81%) was obtained as colourless foam: $[\alpha]_D^{22}$ +3.7° (c 0.1, CH_2Cl_2); IR (KBr) 3468, 3446, 3269, 1734, 1698, 1667, 1609, 1555, 1490, 1461, 1433, 1423, 1296, 1246, 1215, 1173, 1157, 1028, 756; ^1H NMR ($CDCl_3$) δ 8.23 (1H, m), 7.95 (1H, s), 6.95 (4H, m), 5.15 (1H, m), 4.60 (1H, m), 3.98-3.65 (4H, m), 3.89 (3H, s), 2.90 (1H, m), 2.48 (1H, m), 2.25 (1H, m), 2.05-1.65 (2H, m), 1.48 (9H, s).

(4*S*) t-Butyl 6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-7-phenylacetylamino-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262e), was obtained as a white foamy solid (155mg, 53%): mp. 53-7°C; $[\alpha]_D^{22}$ +57.4° (c 0.1, CH_2Cl_2); IR (KBr) 3271, 2978, 1733, 1680, 1437, 1314, 1245, 1156; ^1H NMR ($CDCl_3$) δ 7.46 (1H, s), 7.42-7.20 (5H, m), 5.03 (1H, dd), 4.52-4.40 (1H, m), 3.96-3.70 (2H, m), 3.70-3.49 (1H, m), 3.63 (2H, s), 2.92-2.75 (1H, m), 2.43-2.33 (1H, m), 2.33-2.15 (1H, m), 2.00-1.50 (3H, m), 1.45 (9H, s). Anal. Calcd for $C_{21}H_{28}N_4O_5 \cdot 0.25H_2O$: C, 59.91; H, 6.82; N, 13.31. Found: C, 60.19; H, 6.80; N, 13.30. MS (ES^+) 418 (M^+ + 2, 25%), 417 (M^+ + 1, 100), 362 (9), 361 (45).

262i 263i	
262j 263j	$PhSO_2$—
262k 263k	

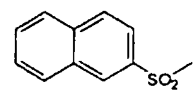
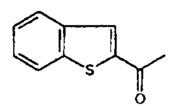
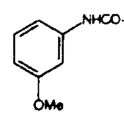
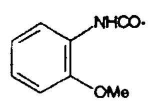
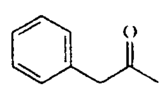
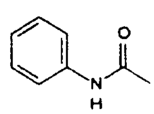
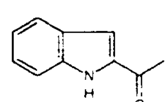
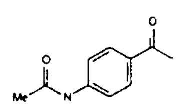
(4*S*) t-Butyl 6,10-dioxo-7-(2-naphthyl)sulfonamide-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262a). 443mg (91%) of the title compound was obtained: mp. 56-7°C; $[\alpha]_D^{25}$ +76° (c 0.15, CH_2Cl_2); IR (KBr) 3429, 2979, 1734, 1675, 1418, 1369, 1339, 1323, 1244, 1164, 665; ^1H NMR ($CDCl_3$) δ 8.45 (1H, s), 8.00-7.59 (7H, m), 4.69-4.65 (1H, m), 4.25-4.12 (1H, m), 4.10-3.99 (1H, m), 3.73-3.55 (2H, m), 2.40-2.30 (1H, m), 1.99-1.91 (1H, m), 1.82-1.62 (2H, m), 1.48-1.46 (2H, m), 1.37 (9H, s). Anal. Calcd for $C_{23}H_{28}N_4O_6S{\bullet}H_2O$: C, 54.53; H, 5.97; N, 11.06. Found: C, 54.60; H, 5.73; N, 10.95. MS (ES^+) 489.

(4*S*) t-Butyl 6,10-dioxo-7-(3-methoxyphenylureido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262c), 120mg (80%) of colourless foam was obtained:



262 263

262a-k 263a-k

compound	R
262a 263a	
262b 263b	
262c 263c	
262d 263d	
262e 263e	
262f 263f	
262g 263g	
262h 263h	

522 (7.15g, 19.1mmol) was dissolved in dichloromethane(100ml), containing dimethylformamide (0.5ml), and cooled to 0°C. Thionyl chloride (1.6ml, 2.61g, 22mmol) and N-ethyl morpholine (4.86ml, 440mg, 38.2mmol) were added and the mixture stirred for 2h. The organic mixture was washed with 2M sodium bisulphate (50ml), saturated sodium bicarbonate (50ml) and brine (50ml), dried ($MgSO_4$) and concentrated. The residues were triturated with ether to give **523** as a white solid (5.73g, 84%): mp. 186-188°C (decomp); $[\alpha]_D^{22}$ +65.3° (c 0.25, CH_2Cl_2); IR (KBr) 3298, 2978, 1750, 1720, 1682, 1658, 1455, 1423, 1369, 1316, 1241, 1212, 1160; ^1H NMR ($CDCl_3$) δ 6.56 (1H, s), 5.17 (1H, dd), 4.48 (1H, bd), 3.81 (3H, m), 3.75 (3H, s), 2.83 (1H, dt), 2.40 (1H, m), 2.28 (1H, m), 1.95 (1H, m), 1.67 (1H, m), 1.47 (9H, s). Anal. Calcd for $C_{15}H_{24}N_4O_6 \cdot 1/6H_2O$: C, 50.13; H, 6.82; N, 15.59. Found: C, 50.12; H, 6.71; N, 15.58. MS (ES^+) 357 (M^+ - 1, 46%), 301 (100%).

(4S) Methyl 7-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (524), was synthesized from **523** via method used to prepare **518**.

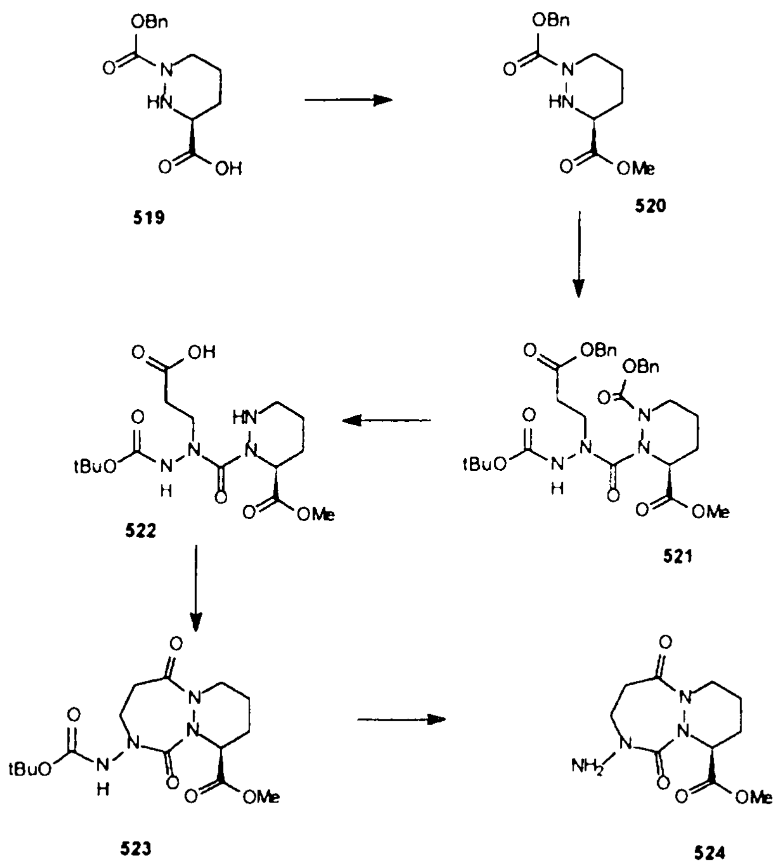
Compounds **262a-k** were synthesized via methods used to prepare **211b-f**.

bd), 3.73 (3H, s), 3.55 (1H, dd), 3.12 (1H, t), 2.06 (1H, m), 1.73 (3H, m). Anal. Calcd for $C_{14}H_{17}N_2O_4 \cdot 0.25H_2O$: C, 59.46; H, 6.59; N, 9.91. Found: C, 59.44; H, 6.46; N, 10.09.

(3*S*) 1-Benzyl 3-methyl 2-(N-2-benzyloxycarbonylethyl-NI-t-butoxycarbonylhydrazino)carbonyl hexahydropyridazine dicarboxylate (521). Using a similar method to that described for **260** above, **521** was prepared, 96% as a crude oil: $[\alpha]_D^{22}$ -22.16° (c 0.25, CH_2Cl_2); IR (film) 3316, 2976, 2953, 1738, 1726, 1714, 1690, 1367, 1260, 1167; ^1H NMR ($CDCl_3$) δ 7.25 (10H, m), 6.82 (1H, bs), 5.10 (4H, m), 4.80 (1H, bs), 4.3-3.4 (6H, m), 3.10 (1H, m), 2.59 (2H, m), 1.95 (2H, m), 1.44 (10H, m + s).

(3*S*) Methyl 2-(N'-t-butoxycarbonyl-N-2-carboxyethylhydrazino)-carbonyl hexahydropyridazine 3-carboxylate (522). Using a similar method to that described for **261** above, **522** was prepared, 92% as a white solid: mp. 146-148°C (decomp); $[\alpha]_D^{22}$ +27.8° (c 0.25, CH_2Cl_2); IR (KBr) 3346, 1740, 1710, 1626, 1497, 1290, 1250, 1206, 1179, 1159; ^1H NMR ($CDCl_3$) δ 7.60 (1H, bs), 7.5-5.5 (1H, vbs), 4.64 (1H, bs), 3.76 (5H, m + s), 3.00 (1H, m), 2.70 (3H, m), 2.16 (1H, m), 1.92 (1H, m), 1.56 (1H, m), 1.46 (11H, m + s). Anal. Calcd for $C_{15}H_{26}N_4O_7$: C, 48.12; H, 7.00; N, 14.96. Found: C, 48.21; H, 6.96; N, 14.86. MS (ES^+) 373 (M^- - 1).

(4*S*) Methyl 7-t-butoxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (523).



(3*S*) Methyl 1-benzyloxycarbonyl-hexahydropyridazine-3-carboxylate (520). **519** (9.4g, 35.6mmol) was suspended in methanol (230ml) and cooled to 0°C in an ice bath. Thionyl chloride (3ml, 4.89g, 41.1mmol) was added dropwise over 30min and the mixture stirred at ambient temperature for 48h. The solvent was removed in vacuo at 30°C and the oily residue dissolved in ethyl acetate (500ml). The organic solution was washed with saturated sodium bicarbonate, water and brine, dried ($MgSO_4$) and concentrated to give **520** (7.84g, 79%) as an oil: $[\alpha]_D^{22}$ -25.9° (c 0.615, CH_2Cl_2); IR (film) 2953, 1739, 1703, 1694, 1440, 1403, 1357, 1261, 1241, 1174; ^1H NMR ($CDCl_3$) δ 7.36 (5H, s), 5.18 (2H, s), 4.00 (1H,

pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (262b), was synthesized via method used to prepare **262** from **261** to give the title compound **262b**, (18.6g, 54%) as an oil: $[\alpha]_D^{20}$ +47.7° (c 0.236, CH_2Cl_2); IR (film) 3291, 2978, 1738, 1727, 1690, 1678, 1439, 1243, 1164; ^1H NMR ($CDCl_3$) δ 6.59 (1H, s), 5.06 (1H, m), 4.47 (1H, m), 3.85 (3H, m), 2.82 (1H, m), 2.37 (1H, m), 2.22 (1H, m), 1.92 (1H, m), 1.63 (2H, m), 1.48 and 1.46 (18H, 2 x s). MS (ES^+) 399 (M^+ + 1).

(4*S*) t-Butyl 7-amino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2,4]triazepine-4-carboxylate (518). Compound **262b** (2.43g, 6.1mmol) was dissolved in 1M hydrogen chloride in ethyl acetate (30ml) and stirred at room temperature for 20h. Solid sodium bicarbonate (4g, 46.5mmol) and water 20ml were added and the mixture stirred for 5min before separating and extracting the aqueous portion with ethyl acetate. The combined organic solution was washed with water, saturated salt, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (50% ethyl acetate in dichloromethane - 100% ethyl acetate) gave the pure product **518** (1.08g, 59%) as an unstable oil: $[\alpha]_D^{20}$ +82° (c 0.55, CH_2Cl_2); IR (film) 3331, 2977, 1731, 1680, 1664, 1439, 1420, 1315, 1158; ^1H NMR ($CDCl_3$) δ 5.08 (1H, m), 4.48 (1H, m), 3.80 (2H, Abq), 3.70 (2H, bs, exch with D_2O), 3.53 (1H, m), 2.75 (1H, m), 2.30 (2H, m), 1.88 (1H, m), 1.71 (2H, m), 1.47 (9H, s).

1254, 1171; ^{1}H NMR ($CDCl_3$) δ 7.35 (5H, m), 6.15 (1H, bs), 5.13 (2H, s), 3.15 (2H, t, J = 6.5), 2.54 (2H, t, J = 6.5), 1.45 (9H, s). Anal. Calcd for $C_{15}H_{22}N_2O_3$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.29; H, 7.51; N, 9.51. MS (ES^+) 295 (M^+ + 1).

(3*S*) 1-Benzyl 3-t-butyl 2-(N-2-benzyloxycarbonylethyl-NI-2-butoxycarbonylhydrazino)carbonyl hexahydropyridazine dicarboxylate (260b), was synthesized via method used to prepare **260** from **259** to afford a gum (81g) which was used in the next step without purification. Analytical data for a pure sample: IR (film) 3318, 2976, 1733, 1451, 1412, 1393, 1366, 1256, 1161; ^{1}H NMR ($CDCl_3$) δ 7.34 (10H, m), 6.68 (0.5H, bs), 5.11 (4H, m), 4.63 (0.5H, bs), 4.14 (1H, m), 3.53 (2H, m), 3.08 (1H, m), 2.63 (2H, m), 2.10-1.60 (4H, m), 1.60-1.35 (19H, m + 2 x s).

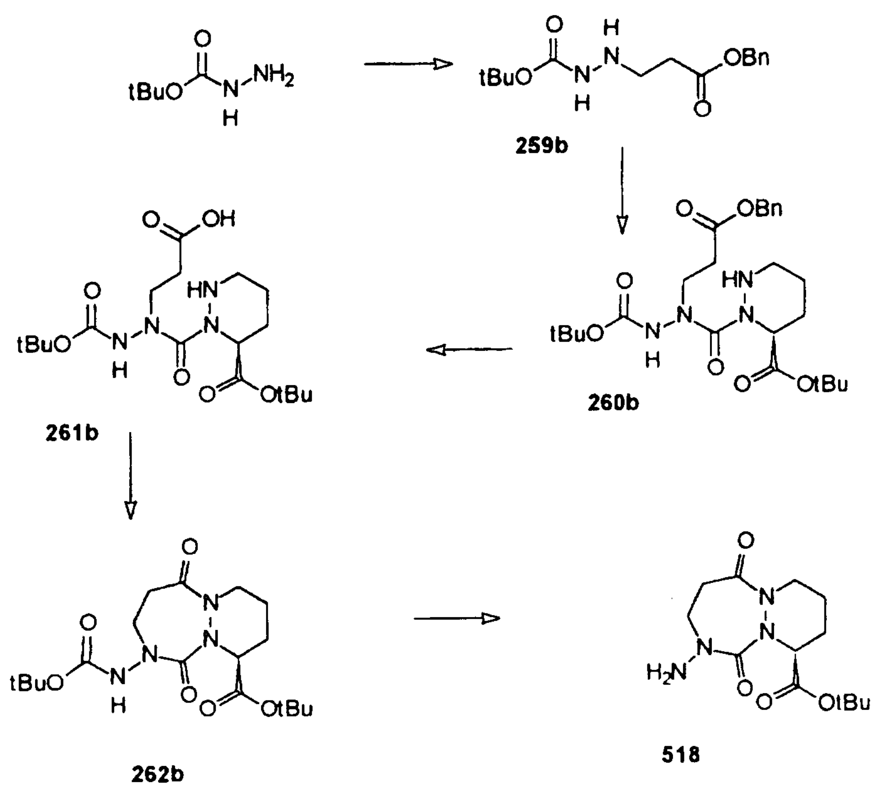
(3*S*) t-Butyl 2-(N'-t-butoxycarbonyl-N-2-carboxyethylhydrazino)-carbonylhexahydropyridazine 3-carboxylate (261b), was synthesized via method used to prepare **261** from **260** to give a gum which was purified by flash chromatography (1:1 ethyl acetate/dichloromethane) to give the title compound **261b** (36.0g, 79.4% over 2 stages): IR (film) 3267, 2979, 2937, 1728, 1668, 1394, 1369, 1245, 1159; ^{1}H NMR ($CDCl_3$) δ 7.6 (1H, bs), 6.8 (1H, vbs), 4.47 (1H, bs), 3.73 (2H, bs), 2.98 (1H, bs), 2.66 (3H, m), 2.04 (1H, bs), 1.84 (1H, m), 1.6-1.2 (21H, m + s).

(4*S*) t-Butyl 7-t-butoxycarbonylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-

Analytical HPLC methods:

(1) Waters DeltaPak C18, 300Å (5µ, 3.9 X 150 mm). Linear acetonitrile gradient (0% - 25%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.

(2) Waters DeltaPak C18, 300Å (5µ, 3.9 X 150 mm). Linear acetonitrile gradient (5% - 45%) containing 0.1% TFA (v/v) over 14 min at 1 mL/min.



Benzyl 3-(N'-t-butyloxycarbonylhydrazino)propionate (259b), was synthesized via method used to prepare **259** from **258** to afford a waxy solid (87g, 51[illegible]): mp 54-55°C; IR (film) 3324, 2978, 1732, 1713, 1455, 1367, 1277,

dimethylformamide (3 X 1 mL) and N-methypyrrolidone (3 X 1 mL).

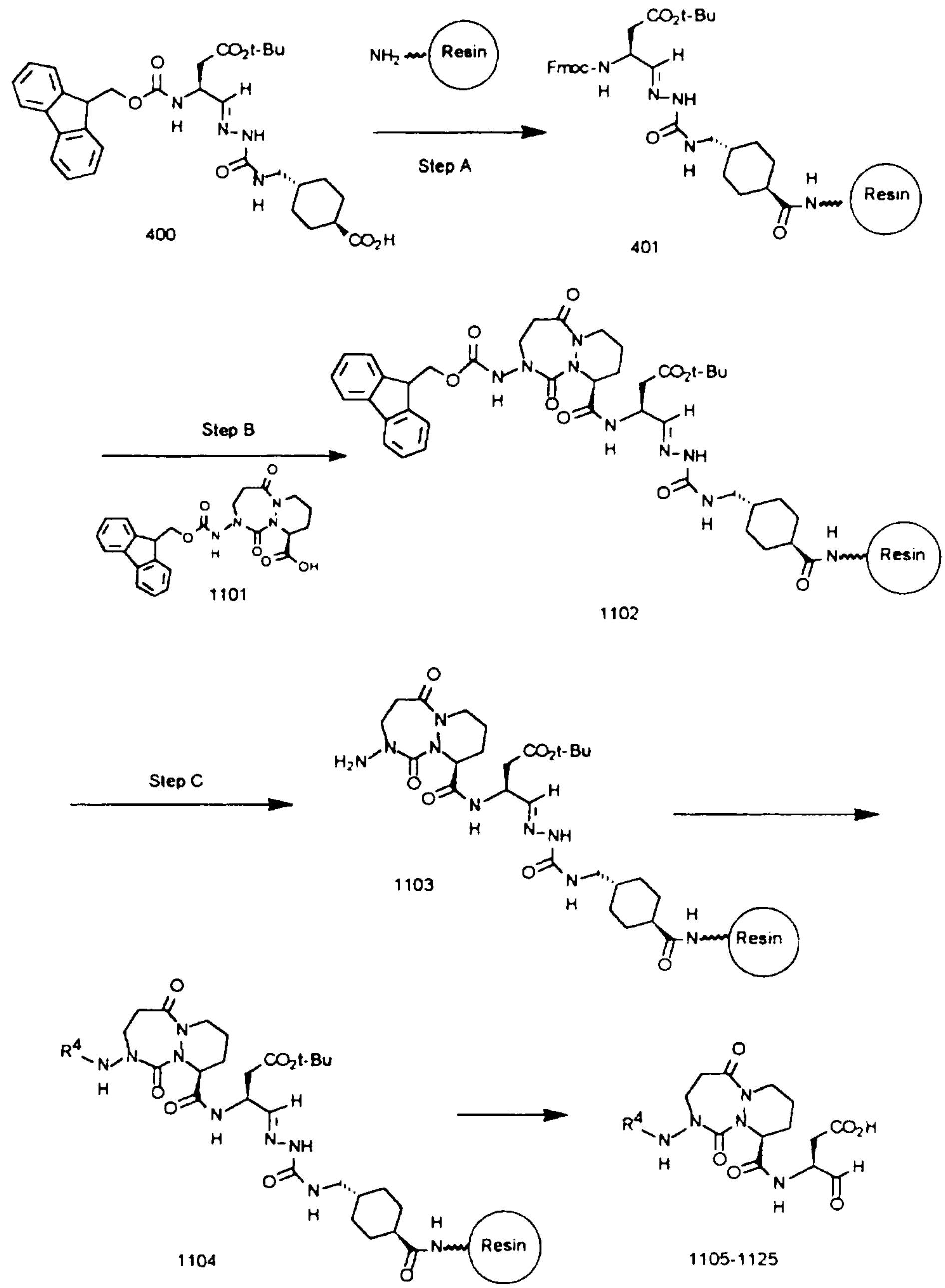
Resin **1103** was acylated with a solution of 0.4M carboxylic acid and 0.4M HOBT in N-methypyrrolidone (0.5 mL), a solution of 0.4M HBTU in N-methylpyrrolidone (0.5 mL) and a solution of 1.6M DIEA in N-methypyrrolidone (0.25 mL) and the reaction was shaken for 2 hr at room temperature. The acylation step was repeated. Finally, the resin was washed with N-methylpyrrolidone (1 X 1 mL), dimethylformamide (4 X 1 mL), dichloromethane (5 X 1 mL) and dried *in vacuo*. The aldehyde was cleaved from the resin and globally deprotected by treatment with 95% TFA/ 5% H_2O (v/v, 1.5 mL) for 30 min at room temperature. After washing the resin with cleavage reagent (1 mL), the combined filtrates were added to cold 1:1 ether:hexane (10 mL) and the resulting precipitate was isolated by centrifugation and decantation. The resulting pellet was dissolved in 10% acetonitrile/90% H_2O/0.1% TFA (5 mL) and lyophilized to obtain crude **1105-1125** as a white powder. The compound was purified by semi-preparative RP-HPLC with a Rainin Microsorb™ C18 column (5 μ, 21.4 X 250 mm) eluting with a linear acetonitrile gradient (8% - 48%) containing 0.1% TFA (v/v) over 30 min at 12 mL/min. Fractions containing the desired product were pooled and lyophilized to provide **1105-1125** (10.8 mg, 63%).

dissolved in DMA (10 mL) and O-benzotriazole-N,N,N,N'-tetramethyluronium hexafluorophosphate (HBTU; 0.88 g, 2.3 mmol), and DIEA (0.8 mL, 4.6 mmol) were added. The solution was transferred to the resin and a further 5 mL DMA added. The reaction mixture was agitated for 1.5 h at room temperature using a wrist arm shaker. The resin was filtered and washed with dimethylacetamide (4 X 15 mL).

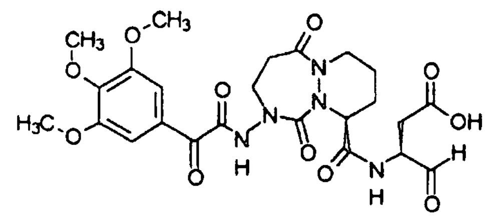
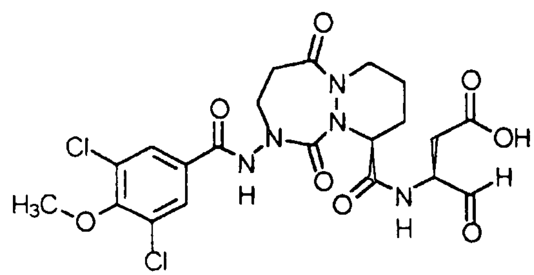
Step B. Synthesis of 1102. Resin **401** was deprotected with 20% (v/v) piperidine/dimethylacetamide (15 mL) for 10 min (shaking) and then for 10 min with fresh piperidine reagent (15 ml). The resin was then washed with dimethylacetamide (6 X 15 ml), followed by N-methypyrrolidone (2 X 25 mL).

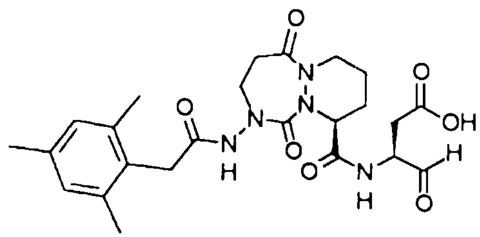
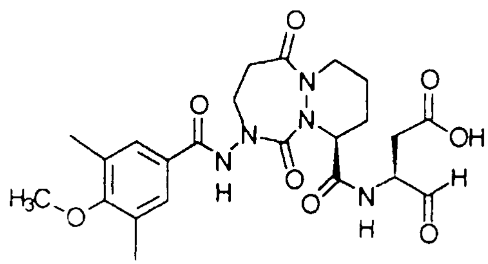
Compound **1101** (0.979 g, 2.11 mmol) was dissolved in dimethylacetamide (8 mL). HBTU (0.81 g, 2.1 mmol) and DIEA (0.75 mL, 4.3 mmol) were added and the solution added to the resin, followed by dimethylacetamide (4 mL). The reaction mixture was agitated for 2 h at room temperature using a wrist arm shaker. The resin work-up was performed as described for **401** to yield **1102**.

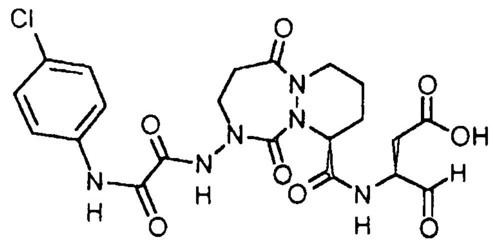
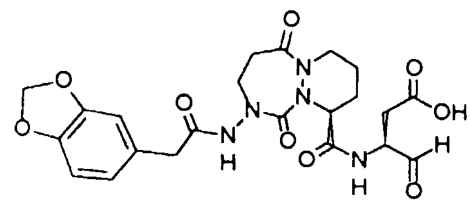
Step C. Synthesis of 1103. This compound was prepared from resin **1102** (0.040 mmol) using an Advanced ChemTech 396 Multiple Peptide synthesizer. The automated cycles consisted of a resin wash with dimethylformamide (2 X 1 mL), deprotection with 25% (v/v) piperidine in dimethylformamide (1 mL) for 3 min followed by fresh reagent (1 mL) for 10 min to yield resin **1103**. The resin was washed with

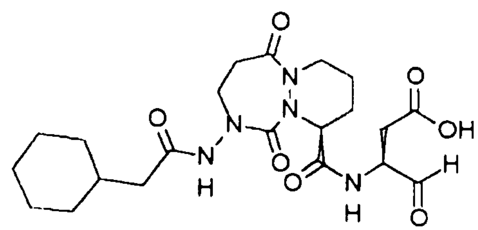
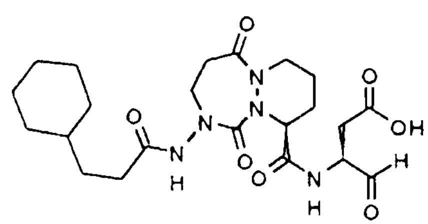


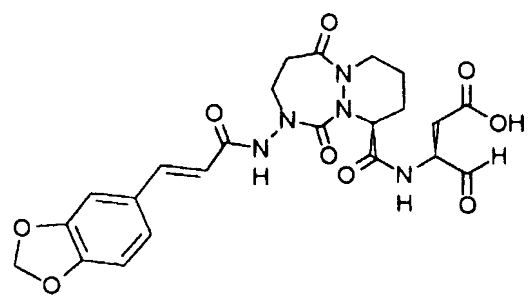
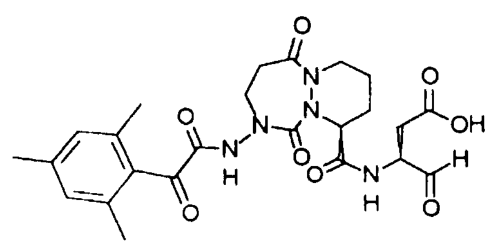
Step A. Synthesis of 401. TentaGel S® NH_2 resin (0.25 mmol/g, 5.25 g) was placed in a sintered glass shaker vessel and washed with dimethylacetamide (3 X 15 mL). Compound **400** (1.36 g, 2.3 mmol) was

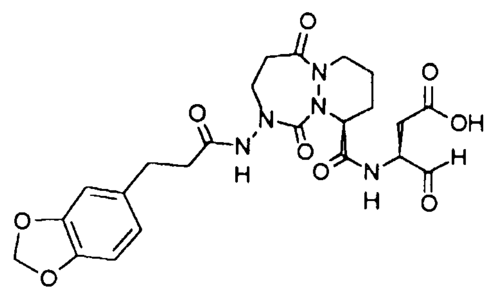
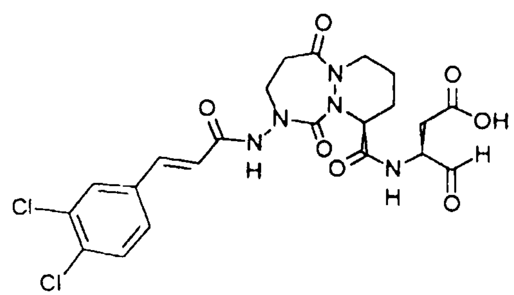
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1124		C24H29N5O11	563.53	13.336 (1) 99%	587
1125		C21H23Cl2N5O8	544.35	8.99 0.95	566

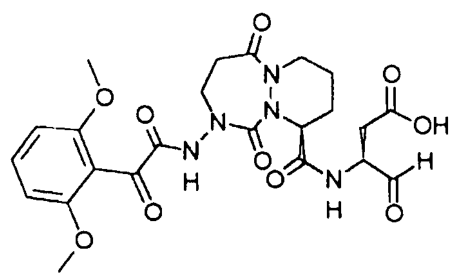
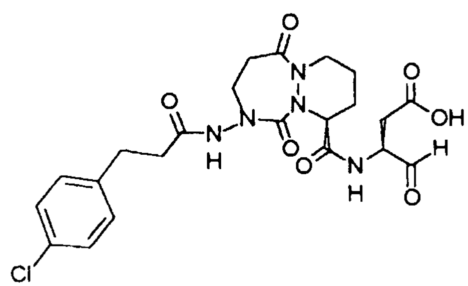
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1122		C24H31N5O7	501.54	10.892 (2) 98%	525.5
1123		C26H24N4O10	552.50	15.85 >0.98	574

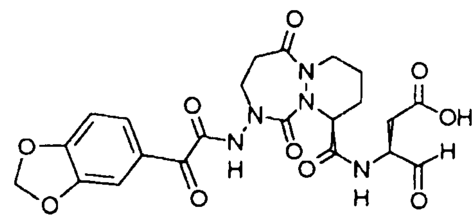
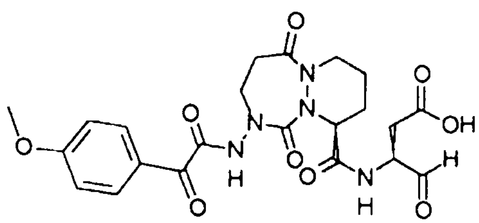
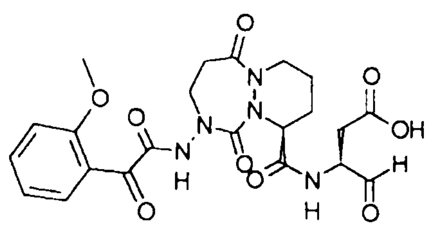
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1120		C21H23ClN6O8	522.91	16.796 (1) 99%	547.3
1121		C22H25N5O9	503.47	11.131 (1) 99%	527.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1118		C21H31N5O7	465.51	13.974 (1) 96%	488.9
1119		C22H33N5O7	479.54	11.079 (2) 95%	502.9

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1116		C23H25N5O9	515.48	14.144 (1) 85%	538.8
1117		C24H29N5O8	515.53	11.551 (2) 97%	538.8

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1114		C23H27N5O9	517.50	12.902 (1) 99%	542.4
1115		C22H23Cl2N5O7	540.36	12.529 (2) 97%	563.4

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1112		C23H27N5O10	533.50	11.377 (1) 98%	557.2
1113		C22H26ClN5O7	507.93	16.317 (1) 98%	531.5

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1109		C22H23N5O10	517.46	12.341 (1) 92%	541.2
1110		C22H25N5O9	503.47	12.991 (1) 96%	527.9
1111		C22H25N5O9	503.47	10.951 (1) 99%	526.7

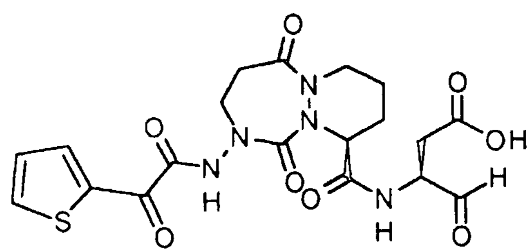
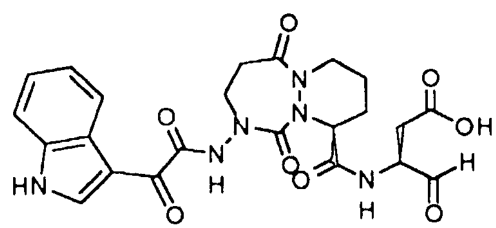
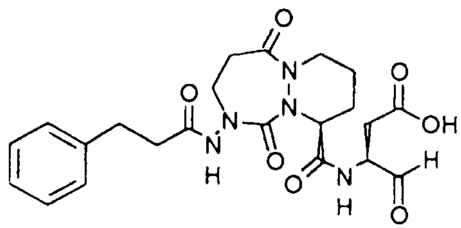
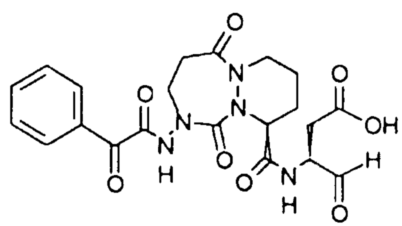
Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1107		C19H21N5O8S	479.47	11.272 (1) 97%	502.9
1108		C23H24N6O8	512.48	13.699 (1) 97%	536.4

Table 24

Compound	Structure	MF	MW	HPLC RT min (method) Purity	MS (M+Na)+
1105		C22H27N5O7	473.49	12.769 (1) 99%	496.9
1106		C21H23N5O8	473.45	12.137 (1) 99%	496.9

(3*S*,4*R*) t-Butyl 3-(allyloxycarbonylamino)4,5-dihydroxy pentanoate (517). A solution **516** (2.44g, 7.41mmol) in 80% aqueous acetic acid (25ml) was stirred at room temperature for 24h then concentrated and azeotroped with toluene (2 x 25ml). The residue was treated with brine (25ml) and extracted with ethylacetate (2 x 25ml). The organic fractions were dried ($MgSO_4$) and concentrated to afford a colourless oil. Flash chromatography (20-80% ethyl acetate in dichloromethane) gave a colourless solid (1.99g, 90%): mp. 74-5°C; $[\alpha]_D^{25}$ -1.3° (c 1.0, CH_2Cl_2); IR (KBr) 1723, 1691; ^1H NMR ($CDCl_3$) δ 6.02-5.78 (2H, m), 5.35-5.16 (2H, m), 4.55 (2H, d), 4.16-4.04 (2H, m), 2.76 (2H, s), 3.56 (2H, m), 2.56 (2H, m), 1.43 (9H, s); Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found : C, 53.79; H, 7.88; N, 4.81; MS(+FAB) 290 (M^++1, 44%), 234 (100).

Example 30

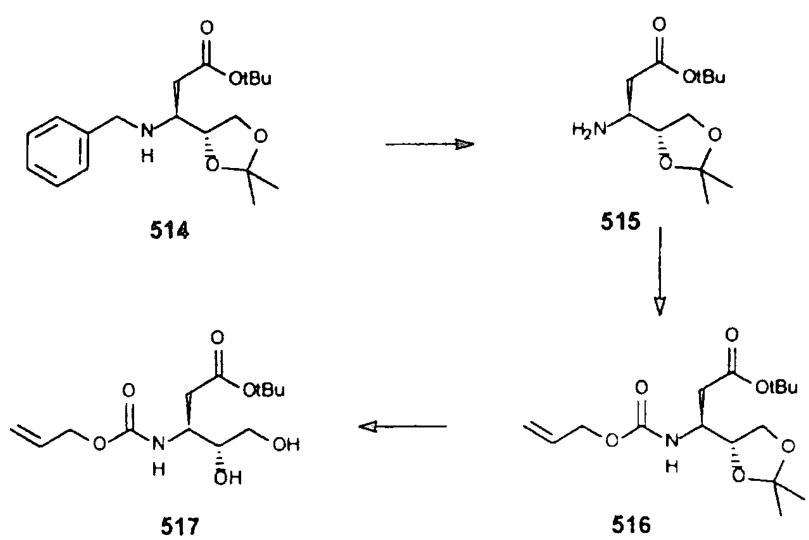
Compounds **1105-1125** were prepared as follows. Physical data for these compounds is listed in Table 24.

Tetrahedron Letters 24, pp. 3009-3012 (1983) as a pure diastereomer (60%) as an oil: $[\alpha]_D^{23}$ -36.9° (c 0.5, dichloromethane); IR (film) 2982, 2934, 1726, 1455, 1369, 1257, 1214, 1157, 1068; ^{1}H NMR ($CDCl_3$) δ 7.31 (5H, m), 4.10 (1H, q, J = 6.0), 4.05-3.75 (4H, m), 3.10 (1H, q, J = 6.0), 2.40 (2H, m), 1.42 (9H, s), 1.40 (3H, s), 1.34 (3H, s).

(3*S*,4*R*) t-Butyl 3-(allyloxycarbonylamino)-4,5-(dimethylmethylenedioxy)pentanoate (516). 514 (3.02g, 9.00mmol) and 10% palladium on carbon (300mg) in ethanol (30ml) were stirred under hydrogen for 2h. The suspension was filtered through celite and a 0.45mm membrane and the filtrate concentrated to give a colourless oil **515** (2.106g, 95%) which was used without purification. The oil (1.93g, 7.88mmol) was dissolved in water (10ml) and 1,4-dioxan and sodium hydrogen carbonate added (695mg, 8.27mmol). The mixture was cooled to 0°C and allyl chloroformate (1.04g, 919ml, 8.66mmol) added dropwise. After 3h the mixture was extracted with ether (2 x 50ml). The combined ether extracts were washed with water (2 x 25ml) and brine (25ml), dried ($MgSO_4$) and concentrated to give a colourless oil. Flash column chromatography (10-35% ethylacetate in hexane) afforded a colourless solid (2.69g, 95%): mp. 64-5°C; $[\alpha]_D^{23}$ -21° (c 1.00, CH_2Cl_2); IR (KBr) 3329, 1735, 1702; ^{1}H NMR ($CDCl_3$) δ 6.00-5.82 (1H, m), 5.36-5.14 (2H, m), 542 (1H, s), 4.56 (1H, d), 4.40-4.08 (2H, m), 4.03 (1H, m) 3.70 (1H, m), 2.52 (2H, m), 1.44 (12H, 2 x s), 1.33 (3H, s); Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found : C, 58.12; H, 8.16; N, 4.19; MS (+FAB) 320 (M^++1, 41%), 274 (70), 216 (100).

486 (M^+ + 1, 33. Accurate mass calculated for $C_{26}H_{32}NO_8$ (MH^+): 486.2128. Found: 486.2121.

(3*S*,4*RS*) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(5-methyl-3-phenylisoxazoloyloxy)pentanoate (513j), was synthesized by a similar method as compound **513g** to afford a pale orange oil (905mg, 91%): IR (film) 3418, 3383, 2980, 1722, 1711, 1601, 1517, 1450, 1424, 1368, 1308, 1252, 1154, 1100, 994, 767, 698; ^{1}H NMR ($CDCl_3$) δ 7.62-7.55 (2H, m), 7.51-7.42 (3H, m), 5.98-5.76 (1H, m), 5.33-5.18 (2H, m), 4.53 (2H, d), 4.18 (2H, d), 3.91 (1H, m), 3.80 (1H, m), 2.76 (3H, s), 2.50 (2H, m), 1.43 (9H, s). Anal. Calcd for $C_{24}H_{30}N_2O_8 \cdot 0.5H_2O$: C, 59.62; H, 6.46; N, 5.79. Found: C, 59.46; H, 6.24; N, 5.72. MS (ES^+) 497 (100%), 475 (M^+ + 1, 15), 419 (48).



(3*S*,4*R*) t-Butyl 3-benzylamino-4,5-(dimethylmethylenedioxy)-pentanoate (514), was prepared by the method described in H. Matsunaga, et al.

(1H, d), 5.30-5.13 (2H, m), 4.51 (2H, d), 4.25 (2H, d), 4.18-4.04 (1H, m), 3.88 (1H, m), 3.50 (1H, m), 2.51 (2H, m), 1.41 (9H, s). MS (ES^+) 508 (57%), 503 (76), 486 (M^+ + 1, 45), 468 (27), 412 (100). Accurate mass calculated for $C_{26}H_{32}NO_8$ (MH^+): 486.2126. Found: 486.2158.

(3*S*,4*R*) t-Butyl (N-allyloxycarbonyl)-3-amino-4-hydroxy-5-(1-naphthoyloxy)pentanoate (513h), was prepared from (3*S*,4*R*) t-butyl (N-allyloxycarbonyl)-3-amino-4,5-dihydroxypentanoate by the method described for **513g** to afford 562mg (85%) of a colourless oil: IR(film) 3418, 2980, 1722, 1711, 1512, 1368, 1278, 1245, 1198, 1157, 1139; ^{1}H NMR ($CDCl_3$) δ 8.90 (1H, d, J = 8.6), 8.21 (1H, dd, J = 1.2, 7.3), 8.04 (1H, d, J = 8.2), 7.89 (1H, dd, J = 1.5, 7.9), 7.67-7.46 (3H, m), 5.88 (1H, m), 5.49 (1H, d, J = 9.0), 5.35-5.18 (2H, m), 4.57-4.46 (4H, m), 4.19 (2H, m), 2.67 (2H, m), 1.40 (9H, s). Anal. Calcd for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.74; H, 6.56; N, 3.09. M.S. (ES^+) 466 (M+Na, 100%), 444 (M+1, 39), 388 (44).

(3*S*,4*RS*) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(3-henoxybenzoyloxy)pentanoate (513i), was synthesized by a similar method as compound **513g** to afford a colourless oil (569mg, 85%): IR (film) 3400, 1723, 1712, 1584, 1528, 1489, 1443, 1367, 1276, 1232, 1190, 1161, 1098, 1074, 995, 755; ^{1}H NMR ($CDCl_3$) δ 8.65-8.59 (1H, d), 7.84-7.66 (2H, m), 7.45-711 (5H, m), 7.05-6.97 (2H, m), 6.00-5.78 (1H, m), 5.54-5.14 (2H, m), 4.62-4.52 (2H, m), 4.42-4.32 (2H, m), 4.08-4.22 (2H, m), 2.78-2.47 (2H, m), 1.44 (9H, s). MS (ES^+) 508 (100%),

dd). Anal. Calcd for $C_{15}H_{17}NO_5 \cdot 0.1H_2O$ C, 61.47; H, 5.91; N, 4.78. Found: C, 61.42; H, 5.88; N, 4.81.

(2*RS*,3*R*) 3-(Allyloxycarbonylamino)-2-ethoxy-5-oxotetrahydrofuran (513f), was synthesized by a similar method as **513d/e** to afford a colourless oil (152mg, 79%): IR (film) 3334, 2983, 2941, 1783, 1727, 1713, 1547, 1529, 1422, 1378, 1331, 1313, 1164, 1122, 1060, 938; ^{1}H NMR ($CDCl_3$) δ 6.09-5.82 (2H, m), 5.50-5.18 (3H, m), 4.64-4.54 (2H, m), 4.27-4.16 (1H, m), 3.95-3.78 (1H, m), 3.73-3.56 (1H, m), 3.05-2.77 (1H, m), 2.56-2.37 (1H, m), 1.35-1.17 (4H, m). Anal. Calcd for $C_{10}H_{15}NO_5$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.16; H, 6.62; N, 5.99. MS (ES^+) 229 (M^+ + 1, 100%).

(3*S*,4*RS*) t-Butyl 3-(allyloxycarbonylamino)-4-hydroxy-5-(2-phenoxybenzoyloxy)pentanoate (513g). 4-Dimethylamino-pyridine (76.0mg, 622mmol) was added to a solution of 2-phenoxybenzoyl chloride (579mg, 2.49mmol) and **517** (600mg, 2.07mmol) in pyridine (10ml). The mixture was stirred at room temperature for 18h before adding brine (25ml) and extracting with ethyl acetate (30ml, 20ml). The combined organic extracts were washed with 1M hydrochloric acid (3 x 25ml), saturated aqueous sodium hydrogen carbonate (2 x 25ml) and brine (25ml), dried ($MgSO_4$) and concentrated. The pale orange oil was purified by flash column chromatography (1-10% acetone in dichloromethane) to afford 447mg (44%) of colourless oil: IR (film) 3375, 2980, 1721, 1712, 1602, 1579, 1514, 1484, 1451, 1368, 1294, 1250, 1234, 1161, 1137, 1081, 754; ^{1}H NMR ($CDCl_3$) δ 7.98-7.93 (1H, m), 7.50-7.41 (1H, m), 7.35-7.25 (2H, m), 7.22-7.03 (3H, m), 6.95 (3H, d), 5.95-5.76 (1H, m), 5.57

(1992)]. Following work-up by extraction with ethylacetate and washing with $NaHCO_3$, the product was dried ($MgSO_4$), filtered and evaporated to yield an oil which contained product and benzyl alcohol. Hexane (200ml) (200ml hexane for every 56g of AllocAsp(CO_2tBu)CH_2OH used) was added and the mixture stirred and cooled overnight. This afforded an oily solid. The liquors were decanted and retained for chromatography. The oily residue was dissolved in ethyl acetate and evaporated to afford an oil which was crystallised from 10% ethyl acetate in hexane (~500ml). The solid was filtered to afford **513d** (12.2g, 19%): mp. 108-110°C; $[\alpha]_D^{24}$ +75.72° (c 0.25, CH_2Cl_2); IR (KBr)3361, 1778, 1720, 1517, 1262, 1236, 1222, 1135, 1121, 944, 930, 760; ^{1}H NMR ($CDCl_3$) δ 7.38 (5H, m), 5.90 (1H, m), 5.50 (1H, s), 5.37 (0.5H, m), 5.26 (2.5H, m), 4.87 (1H, ABq), 4.63 (3H, m), 4.31 (1H, m), 3.07 (1H, dd), 2.46 (1H, dd). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.85; H, 5.89; N, 4.80.

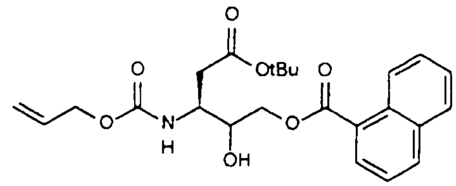
The liquors were combined and evaporated to yield an oil (~200g) containing benzyl alcohol. Hexane/ethyl acetate (9:1, 100ml) was added and the product purified by chromatography eluting with 10% ethyl acetate in hexane to remove the excess benzyl alcohol, and then dichloromethane/hexane (1:1 containing 10% ethyl acetate). This afforded **513e** containing some **513d** (20.5g, 32%): mp. 45-48°C; $[\alpha]_D^{24}$ -71.26° (c 0.25, CH_2Cl_2); IR (KBr) 3332, 1804, 1691, 1536, 1279, 1252, 1125,976. ^{1}H NMR ($CDCl_3$) δ 7.38 (5H, m), 5.91 (1H, m), 5.54 (1H, d, J = 5.2), 5.38 (3H, m); 4.90 (1H, ABq); 4.60 (4H, m), 2.86 (1H, dd); 2.52 (1H,

m), 4.59-4.56 (2H, m), 4.32-3.96 (2H, m), 3.85-3.73 (1H, m), 3.02-2.76 (3H, m), 2.49-2.34 (1H, m).

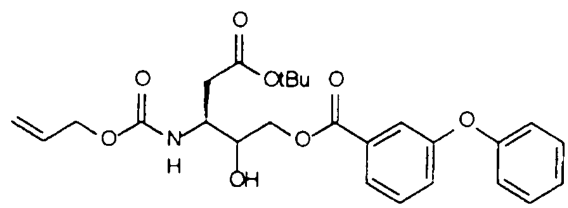
(2*RS*,3*S*) 3-(Allyloxycarbonyl)amino-2-cyclopentyloxy-5-oxotetrahydrofuran (513b), was prepared as **513d/e** to afford 8g (51%) of a mixture of diastereoisomers as a clear oil: $[\alpha]_D^{20}$ -13° (c 0.25, CH_2Cl_2); IR (KBr) 3325, 2959, 2875, 1790, 1723, 1535, 1420, 1328, 1257, 1120, 1049, 973, 937; ^1H NMR ($CDCl_3$) δ 6.02-5.80 (1H, m), 5.53-5.46 (2H, m), 5.37-5.21 (2H, m), 4.58 (2H, d, J = 5.5), 4.50-4.46 (0.5H, m), 4.34-4.25 (1H, m), 4.19-4.12 (0.5H, m), 3.06-2.77 (1H, m), 2.53-2.35 (1H, m), 1.85-1.50 (8H, m). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20. Found: C, 56.62; H, 7.22; N, 4.95. MS (ES^+) 270.

(2*R*,3*S*) 3-Allyloxycarbonylamino-2-(indan-2-yloxy)-5-oxotetrahydrofuran (513c), was synthesized by a similar method as compound **513d/e** to afford a single isomer (20%) as a pale yellow oil: $[\alpha]_D^{24}$ -63.1° (c 0.2, CH_2Cl_2); IR (film) 3338, 2948, 1791, 1723, 1529, 1421, 1330, 1253, 1122, 984, 929, 746; ^1H NMR ($CDCl_3$) δ 7.20 (4H, m), 5.87 (1H, m), 5.61 (1H, d, J = 5.4), 5.33-5.10 (2H, m), 4.70 (1H, m), 4.56 (3H, m), 3.33-3.19 (2H, m), 3.10-2.94 (2H, m), 2.81 (1H, dd, J = 8.3, 17.3), 2.43 (1H, dd, J = 10.5, 17.3).

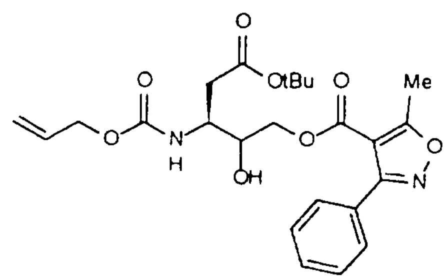
(2*R*,3*S*) 3-Allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydro-furan (513d) and (2*S*,3*S*) 3-Allyloxycarbonylamino-2-benzyloxy-5-oxo-tetrahydrofuran (513d/e), were prepared [via method described by Chapman Biorg. & Med. Chem. Lett., 2, pp. 615-618



513h

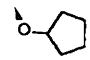
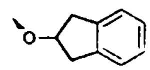
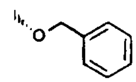
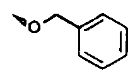


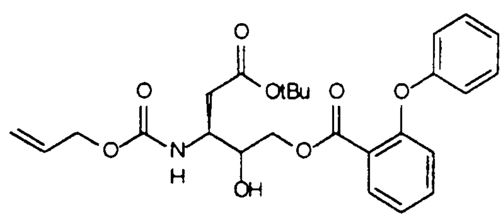
513i



513j

(2*RS*,3*S*) 3-(Allyloxycarbonyl)amino-2-(2-phenethyloxy)-5-oxotetrahydrofuran (513a), was prepared by a similar method as compound **513d/e** to afford a mixture of diastereoisomers (670mg, 50%) as an oil: IR (KBr) 3331, 2946, 1790, 1723, 1713, 1531, 1329, 1257, 1164, 1120, 1060, 977, 937, 701; ^{1}H NMR ($CDCl_3$) δ 7.36-7.18 (5H, m), 5.99-5.83 (1H, m), 5.41-5.34 (2H, m), 5.28-5.18 (2H,

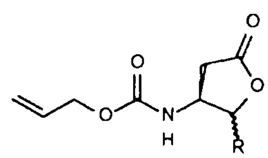
513b-2	
513c	
513d	
513e	
513f	
513f-1	
513f-2	



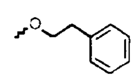
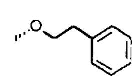
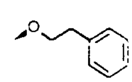
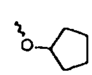
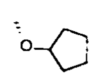
513g

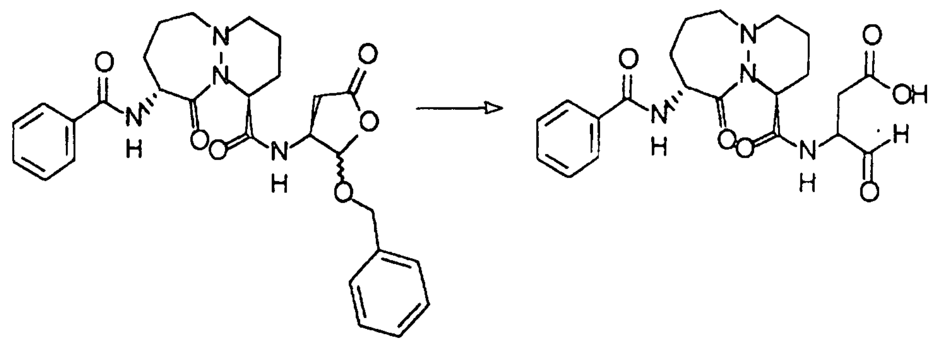
104mg (33%) of a white powder: mp. 115-119°C; $[\alpha]_D^{24}$ -19.8° (c 0.2 MeOH); IR (KBr) 3293, 2944, 1786, 1639, 1578, 1537, 1489, 1450, 1329, 1162, 1124; ^{1}H NMR (CD_3OD) δ 7.85 (2H, d, J = 7.0), 7.49 (3H, m), 5.49 (1H, m), 4.55 (1H, m), 4.30 (2H, m), 3.40 (1H, m), 3.19-2.89 (3H, m), 2.63 (2H, m), 2.16-1.81 (5H, m), 1.60 (3H, m). Anal. Calcd for $C_{21}H_{26}N_4O_6 \cdot H_2O$: C, 56.24; H, 6.29; N, 12.49. Found: C, 56.54; H, 6.05; N, 12.29. MS (ES$^+$) 429 (M - 1, 100%).

Compounds **513a-j** were prepared as described below.



513a-f

compound	R
513a	
513a-1	
513a-2	
513b	
513b-1	



245b 246b

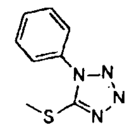
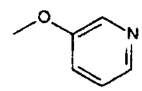
[1*S*,9*R*(2*RS*,3*S*)] 9-Benzoylamino-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-1,2,3,4,7,8,9,10-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamide (245b), was prepared from (1*S*,9*R*) 9-Benzoylamino-1,2,3,4,7,8,9,10-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid by the method described for **245** to afford 416mg (85%) of a colourless foam (~1:1 mixture of diastereoisomers): IR (KBr) 3392, 3302, 2942, 1792, 1642, 1529, 1520, 1454, 1119; ^{1}H NMR ($CDCl_3$) δ 7.79 (2H, m), 7.51-7.09 (10H, m), 5.52 (0.5H, d, J = 5.3), 5.51 (0.5H, s), 5.36 (1H, m), 4.84 (1H, m), 4.74-4.59 (1.5H, m), 4.51 (1H, m), 4.38 (0.5H, m), 3.22-2.83 (5H, m), 2.51 (1H, m), 2.25 (2H, m), 2.01-1.46 (6H, m). Anal. Calcd for $C_{28}H_{32}N_4O_6 \cdot 0.75H_2O$: C, 62.97; H, 6.32; N, 10.49. Found: C, 63.10; H, 6.16; N, 10.21. MS (ES$^+$) 521 (M + 1, 100%).

[3*S*(1*S*,9*R*)] 3-(9-Benzoylamino-1,2,3,4,7,8,9,10-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (246b), was prepared from **245b** by the method described for **246** to afford

1728, 1659, 1531, 1501, 1415, 1341, 1278, 1253, 1222, 1185; ^{1}H NMR ($CDCl_3$) δ 8.05 (1H, d, J = 7.9), 7.57 (5H, br s), 5.30 (1H, m), 5.01 (2H, m), 4.70-4.10 (4H, m), 3.40-2.85 (4H, m), 2.62 (1H, m), 2.33 (1H, m), 2.27-1.65 (5H, m), 2.01 (3H, s).

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(3-pyridyloxy)pentanoate (512b), was prepared by a similar method as compound **509b**, to afford (9%) as a colourless foam: IR (KBr) 3333, 1727, 1661, 1542, 1427, 1369, 1279, 1257, 1232, 1156; ^{1}H NMR ($CDCl_3$) δ 8.30 (2H, m), 7.20 (3H, m), 6.45 (1H, d, J = 7.4), 5.17 (1H, m), 4.91 (3H, m), 4.55 (1H, m), 3.27 (1H, m), 3.14-2.70 (4H, m), 2.41 (1H, m), 2.04 (3H, s), 2.10-1.65 (6H, m), 1.44 (9H, s).

[3*S*(1*S*,9*S*)] 3-(9-Acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(3-pyridyloxy)pentanoic acid (283d), was prepared by a similar method as compound **280**. (100%) as a colourless foam: $[\alpha]_D^{22}$ -106.0° (c 0.2, 10% CH_3OH/CH_2Cl_2); IR (KBr) 3312, 1735, 1664, 1549, 1426, 1279, 1258, 1200, 1135; ^{1}H NMR ($CDCl_3$) δ 8.27 (2H, m), 7.46 (2H, m), 5.09 (1H, m), 4.79 (3H, m), 4.47 (1H, m), 3.40 (1H, m), 3.30-2.70 (3H, m), 2.54 (1H, m), 2.30 (1H, m), 1.98 (3H, s), 2.05-1.65 (4H, m).

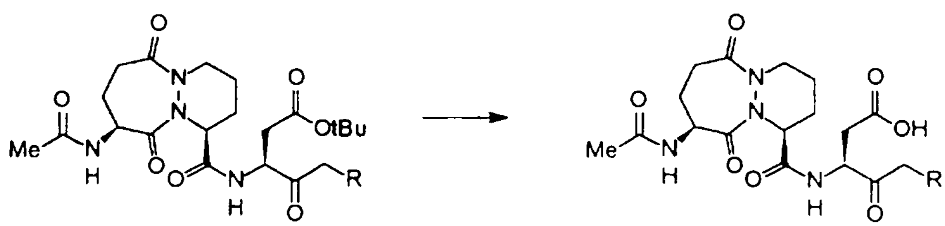
compound	R
512a **280d**	
512b **283d**	

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1H-tetrazole-5-thio)pentanoate (512a), was prepared by a similar method as compound **509b**, to afford (83%) as a colourless foam: $[\alpha]_D^{23}$ -129.6° (c 0.1, CH_2Cl_2); IR (KBr) 3323, 1726, 1664, 1531, 1501, 1444, 1415, 1394, 1369, 1279, 1254, 1156; ^1H NMR ($CDCl_3$) δ 7.59 (5H, s), 7.37 (1H, d, J = 7.9), 6.38 (1H, d, J = 7.4), 5.27 (1H, m), 4.98 (2H, m), 4.58 (2H, d + m), 4.28 (1H, d, J = 17.2), 3.28 (1H, m), 3.10-2.65 (4H, m), 2.31 (2H, m), 2.03 (3H, s), 2.10-1.72 (4H, m), 1.48 (9H, s).

[3*S*(1*S*,9*S*)] 3-(9-Acetamido-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1H-tetrazole-5-thio)pentanoic acid (280d), was prepared by a similar method as compound **280**, to afford (77%) as a colourless foam: $[\alpha]_D^{22}$ -93.3° (c 0.1, CH_2Cl_2); IR (KBr) 3316,

7.20 (2H, s), 5.91 (1H, d), 5.24-5.16 (1H, m), 5.07-4.86 (3H, m), 4.81-4.51 (2H, m), 3.67 (3H, s), 3.34-3.16 (1H, m), 3.10-2.81 (3H, m), 2.72-2.54 (1H, m), 2.41-2.31 (1H, m), 2.07-1.62 (5H, m), 1.47 (9H s). MS (ES^+) 562 (M^+ + 1, 100%), 506 (38).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridinyloxy)pentanoic acid (283c), was synthesized by a similar method as compound **280** to afford an off-white powder (167mg, 98%): mp. 90-105°C; $[\alpha]_D^{22}$ -106° (c 0.11 MeOH); IR (KBr) 3325, 3070, 2956, 1669, 1544, 1423, 1256, 1199, 1133, 1062; ^{1}H NMR (D_6-DMSO) δ 8.95 (1H, d), 8.45-8.20 (2H, m), 7.53-7.45 (3H, m), 5.19-5.08 (3H, m), 4.70-4.62 (1H, m), 4.41-4.30 (2H, m), 3.53 (3H, s), 2.92-2.68 (3H, m), 2.22-2.06 (2H, m), 1.95-1.82 (2H, m), 1.63-1.53 (1H, m). MS (ES^+) 506 (M^+ + 1, 100%).



512a, 512b **280d, 283d**

1688, 1527, 1501, 1458, 1418, 1368, 1279, 1250, 1155, 1064; ^{1}H NMR ($CDCl_3$) δ 7.70 (1H, d), 7.63-7.53 (5H, m), 5.84 (1H, d), 5.34-5.27 (1H, m), 5.05-4.92 (1H, m), 4.78-4.54 (3H, m), 4.38 (1H, d), 3.66 (3H, s), 3.37-3.19 (1H, m), 3.07-2.94 (1H, m), 2.91-2.82 (2H, m), 2.71-2.56 (1H, m), 2.40-2.30 (1H, m), 2.19-2.13 (1H, m), 2.08-1.68 (4H, m), 1.42 (9H, s). MS (ES^+) 667 (31%), 645 (M^+ + 1, 100), 589 (62).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-[5-(1-phenyltetrazolyl)-thio]pentanoic acid (280c), was synthesized by a similar method as compound **280** to afford a pale cream solid (203mg, 88%): mp. 105-130°C; $[\alpha]_D^{22}$ -235° (c 0.11 MeOH); IR (KBr) 3342, 2951, 1727, 1667, 1529, 1501, 1459, 1416, 1276, 1252, 1225, 1192, 1062; ^{1}H NMR (D_6-DMSO) δ 8.89 (1H, d), 7.69 (5H, s), 7.50 (1H, d), 5.18-5.11 (1H, m), 4.79-4.69 (1H, m), 4.57 (2H, s), 4.42-4.32 (1H, m), 3.54 (3H, s), 2.92-2.63 (3H, m), 2.21-1.82 (5H, m), 1.65-1.57 (1H, m). MS (ES^+) 587 (M - 1, 100%).

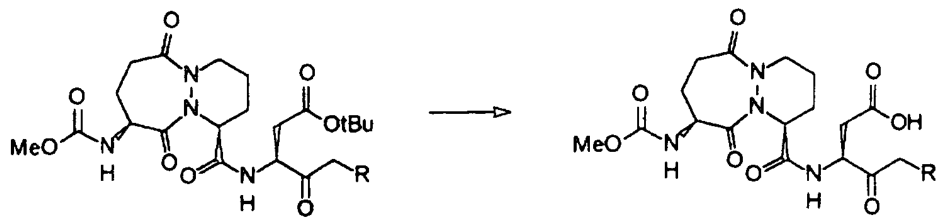
[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridinyloxy) pentanoate (508e), was synthesized by a similar method as compound **509b** to afford a pale orange solid (199mg, 25%): mp. 80-120°C; $[\alpha]_D^{23}$ -89° (c 0.51 CH_2Cl_2); IR (KBr) 3333, 2978, 1726, 1669, 1578, 1536, 1478, 1426, 1368, 1277, 1253, 1232, 1155, 1064; ^{1}H NMR ($CDCl_3$) δ 8.41-8.18 (2H, m), 7.81 (1H, d), 7.26-

1383, 1253, 1155, 1064; ^1H NMR ($CDCl_3$) δ 8.49 (2H, d, J = 4.8), 7.13 (1H, d, J = 7.9), 7.03-6.98 (1H, m), 5.47 (1H, d, J = 7.9), 5.23-5.19 (1H, m), 5.09-5.01 (1H, m), 4.84-4.51 (2H, m), 4.04 (2H, AB), 3.69 (3H, s), 3.38-3.19 (1H, m), 3.06-2.64 (4H, m), 2.40-1.76 (6H, m), 1.43 (9H, s). Anal. Calcd for $C_{25}H_{34}N_6O_8S$: C, 51.89; H, 5.92; N, 14.52. Found: C, 51.49; H, 6.04; N, 13.87. MS (ES^+) 579.

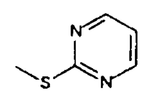
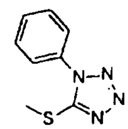
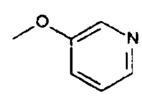
[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methoxycarbonyl)-amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(2-mercaptopyrimidine)-4-oxopentanoic acid (511c), was prepared by a similar method as compound **280** to afford 370mg (79%) of a white powder: mp. 105°C (dec); $[\alpha]_D^{22}$ -94° (c 0.20, CH_2Cl_2); IR (KBr) 3316, 3057, 2957, 1724, 1664, 1252, 1416, 1384, 1254, 1189, 1063; ^1H NMR (D_6-DMSO) δ 8.85 (1H, d, J = 7.8), 8.62 (2H, d, J = 4.7), 7.53 (1H, d, J = 8.0), 7.28-7.23 (1H, m), 5.21-5.17 (1H, m), 4.87-4.79 (1H, m), 4.47-4.35 (2H, m), 4.23 (2H, AB), 3.58 (3H, s), 3.30-3.21 (1H, m), 2.95-2.50 (4H, m), 2.35-1.60 (6H, m). Anal. Calcd for $C_{21}H_{26}N_6O_8S \cdot H_2O$: C, 46.66; H, 5.22; N, 15.55. Found: C, 46.66; H, 5.13; N, 15.07. MS (ES^+) 523, (ES^+) 521.

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonylamino)-1,2,3,4,7,8,9,10-octahydro—6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-[5-(1-phenyltetrazolyl)-thio]pentanoate (508d), was synthesized by a similar method as compound **509b** to afford a colourless solid (269mg, 87%): mp. 80-110°C; $[\alpha]_D^{23}$ -108° (c 0.60 CH_2Cl_2); IR (KBr) 3315, 2977, 1727,

5.32 (2H, m), 4.83 (2H, m), 4.45 (2H, m), 3.43-2.77 (4H, m), 2.97 (3H, s), 2.42 (2H, m), 2.05-1.72 (5H, m).



508c-e **511c, 280c, 283c**

compound	R
508c **511c**	
508d **280c**	
508e **283c**	

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(2-mercaptopyrimidine)-4-oxo-pentanoate (508c), was prepared by a similar method as compound **509b** to afford 544mg (97%) of a pale yellow foam: $[\alpha]_D^{20}$ -86° (c 0.19, CH_2Cl_2); IR (KBr) 3426, 2947, 1725, 1669, 1551, 1418,

was prepared by a similar method as compound **280**, (100%) as a colourless foam: mp. 120-5°C; $[\alpha]_D^{25}$ -112.4° (c 0.1, CH_2Cl_2); IR (KBr) 3328, 1730, 1664, 1529, 1501, 1410, 1328, 1277, 1219, 1153, 1134, 991; ^1H NMR ($CDCl_3$) δ 8.07 (1H, d, J = 7.8), 7.58 (5H, s), 6.41 (1H, d, J = 9.5), 5.32 (1H, m), 5.04 (1H, m), 4.70 (1H, d, J = 17.5), 4.60 (3H, m), 3.50-2.9 (3H, m), 2.98 (3H, s), 2.45 (2H, m), 2.06 (4H, m), 1.68 (1H, m).

[3*S*(1*S*,9*S*)] t-Butyl 3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(3-pyridyloxy)pentanoate (504h), was prepared by a similar method as compound **509b** (24%) as a colourless foam: $[\alpha]_D^{23}$ -101.0° (c 0.2, CH_2Cl_2); IR (KBr) 3330, 1727, 1669, 1425, 1396, 1369, 1328, 1276, 1256, 1231, 1155, 1137, 991; ^1H NMR ($CDCl_3$) δ 8.28 (2H, br d, J = 9.4), 7.71 (1H, d, J = 7.9), 7.22 (2H, s), 6.03 (1H, d, J = 9.4), 5.36 (1H, m), 4.95 (2H, m), 4.52 (2H, m), 3.29 (1H, m), 3.07 (3H, s), 3.23-2.75 (3H, m), 2.66-2.35 (2H, m), 2.30-1.60 (5H, m), 1.42 (9H, s).

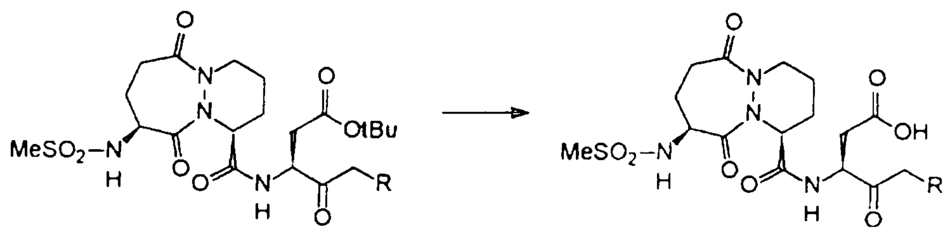
[3*S*(1*S*,9*S*)] 3-(6,10-Dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(3-pyridyloxy)pentanoic acid (283b), was prepared by a similar method as compound **280**, (100%) as a colourless foam: mp. 120-5°C ; $[\alpha]_D^{25}$ -85.2° (c 0.1, 10% CH_3OH/CH_2Cl_2); IR (KBr) 3337, 1738, 1667, 1560, 1457, 1424, 1326, 1317, 1278, 1258, 1200, 1189, 1150, 1133, 991; ^1H NMR ($CDCl_3/CD_3OD$) δ 8.35 (2H, m), 7.54 (2H, m),

(methylsulphonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (505f), was prepared by a similar method as compound **508a** using **507b** and 3-chloro-2-hydroxy-4H-pyrido[1,2-a]pyrimidin-4-one and directly followed by the hydrolysis of **504f** with trifluoroacetic to afford a tan powder (65mg, 30%): $[a]_D^{20}$ -128° (c 0.10, MeOH); IR (KBr) 3414, 2928, 1667, 1527, 2459, 1407, 1328, 1274, 1153, 1134; ^{1}H NMR (MeOD) δ 9.35 (1H, d, J = 6.6H), 8.34 (1H, t, J = 7.2H), 7.99-7.95 (1H, m), 7.76-7.69 (1H, m), 5.85-5.45 (3H, m), 5.30-5.21 (1H, m), 4.93-4.66 (2H, m), 3.81-3.65 (1H, m), 3.66 (3H, m), 3.45-2.52 (4H, m), 2.52-1.71 (6H, m). D.J. Hlasta et al., J. Med. Chem. 1995, 38, 4687-4692.

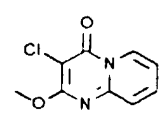
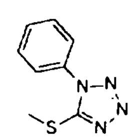
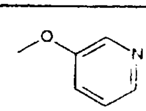
[3*S*(1*S*,9*S*)] t-Butyl 3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio)pentanoate (504g), was prepared by a similar method as compound **509b**, (83%) as a colourless foam: $[\alpha]_D^{23}$ -112.7° (c 0.2, CH_2Cl_2); IR (KBr) 3312, 1726, 1668, 1501, 1413, 1395, 1369, 1328, 1276, 1254, 1155; ^{1}H NMR ($CDCl_3$) δ 7.59 (5H, m), 7.48 (1H, d, J = 8.0), 5.68 (1H, d, J = 9.0), 5.37 (1H, m), 4.95 (1H, m), 4.62-4.31 (4H, m), 3.36 (1H, m), 2.98 (3H, s), 2.88 (4H, m), 2.66 (1H, m), 2.42 (2H, m), 1.98 (1H, m), 1.75 (1H, m), 1.43 (9H, s).

[3*S*(1S,9S)] 3-(6,10-Dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio)pentanoic acid (280b),

(1H, d), 7.87 (2H, d), 7.54-7.42 (3H, m), 6.48 (1H, d), 5.22-5.15 (1H, m), 4.57-4.46 (1H, m), 3.62-3.41 (1H, m), 3.22-3.13 (1H, m), 3.02-2.81 (2H, m), 2.70-1.80 (6H, m). Anal. Calcd for $C_{26}H_{28}N_6O_8 \cdot 1.5H_2O$: C, 54.30; H, 5.35; N, 14.61. Found: C, 54.14; H, 5.35; N, 13.04. MS (ES^+) 551 (M - 1, 100%). Accurate mass calculated for $C_{26}H_{29}N_6O_8$ (MH^+): 553.2047. Found: 553.2080.



504f-h 505f, 280b, 283b

compound	R
504f 505f	
504g 280b	
504h 283b	

[3*S*(1*S*,9*S*)] 5-(3-Chloro-2-oxy-4H-pyrido[1,2-a]pyrimidin-4-one)-3-[6,10-dioxo-9-

(3-pyridyloxy)pentanoic acid (283), was prepared by a similar method as compound **280** to afford a colourless foam (100%): mp. ~125°C; $[\alpha]_D^{19}$ -84.1° (c 0.1, 20% MeOH/CH_2Cl_2); IR (KBr) 3401, 1736, 1663, 1538, 1489, 1459, 1425, 1281, 1258, 1200, 1134; ^{1}H NMR ($CD_3OD/CDCl_3$) δ 8.38 (2H, m), 7.84-7.40 (8H, m), 5.16 (4H, m), 4.80 (1H, m), 4.56 (1H, m), 3.50 (1H, m), 3.12 (2H, m), 2.82 (2H, m), 2.37 (1H, m), 2.10-1.65 (5H, m). Anal. Calcd for $C_{27}H_{29}N_5O_8 \cdot 0.4H_2O$: C, 51.77; H, 4.61; N, 10.41. Found: C, 52.19; H, 4.93; N, 9.99.

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-9-(phenycarbonylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-{2-[4(3H)-pyrimidone]}pentanoate (509d), was synthesized by a similar method as compound **509b** to afford a colourless solid (49.6mg, 82%): ^{1}H NMR ($CDCl_3$) δ 8.02 (1H, s), 7.95-7.86 (1H, m), 7.84-7.76 (2H, m), 7.62-7.35 (4H, m), 7.22-7.07 (1H, m), 6.43 (1H, d), 5.26-5.08 (2H, m), 5.03-4.72 (3H, m), 4.66-4.50 (1H, m), 3.43-3.19 (1H, m), 3.15-2.97 (1H, m), 2.86-2.72 (3H, m), 2.48-2.31 (1H, m), 2.18-1.60 (6H, m), 1.43 (9H, s).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-1,2,3,4,7,8,9,10-octahydro-9-(phenycarbonylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-{2-[4(3H)-pyrimidone]}pentanoic acid (510d), was synthesized by a similar method as compound **280** to afford a colourless solid (25.7mg, 57%): mp. 140-80°C; IR (KBr) 3391, 2945, 1733, 1664, 1530, 1422, 1363, 1277, 1259, 1204; ^{1}H NMR (CD_3OD) δ 8.23 (1H, s), 7.94

room temperature for 30min before evaporation under reduced pressure. The residue was triturated with dry toluene and evaporated. Chromatography on silica gel eluting with 10% methanol in dichloromethane gave a colourless glass which was crystallised from dichloromethane/diethyl ether to give 62mg (69%) of colourless solid: mp. 145°C (decomp.); $[\alpha]_D^{22}$ -80.9° (c 0.1, CH_2Cl_2); IR (KBr) 3400, 1727, 1658, 1530, 1501, 1460, 1445, 1416, 1280, 1254; ^1H NMR ($CDCl_3$) δ 8.00 (1H, m), 7.79 (2H, d, J = 6.7), 7.58-7.30 (9H, m), 5.25 (2H, m), 4.94 (1H, m), 4.53 (2H, m), 4.35 (1H, m), 3.35 (1H, m), 3.01 (3H, m), 2.73 (1H, m), 2.38 (1H, m), 1.98 (4H, m), 1.64 (1H, m). Anal. Calcd for $C_{29}H_{30}N_8O_7S{\cdot}0.2TFA$: C, 53.71; H, 4.63 N, 17.04. Found: C, 53.97; H, 4.92; N, 16.77. MS (ES^+) 633.55 (M^+ - 1).

[3*S*(1*S*,9*S*)] t-Butyl 3-[9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-pyridyloxy)pentanoate (509c), was prepared by a similar method as compound **509b** to afford a colourless glass (34%): $[\alpha]_D^{22}$ -77.1° (c 0.25, CH_2Cl_2); IR (film) 3311, 1724, 1658, 1603, 1578, 1536, 1488, 1458, 1426, 1368, 1340, 1279, 1256, 1231, 1155, 707; ^1H NMR ($CDCl_3$) δ 8.29 (2H, m), 7.84 (2H, m), 7.48 (4H, m), 7.22 (3H, m), 5.20 (2H, m), 4.90 (2H, m), 4.58 (1H, m), 3.29 (1H, m), 3.20-2.70 (4H, m), 2.38 (2H, m), 1.96 (4H, m), 1.68 (1H, m), 1.42 (9H, s). MS (ES^+) 608.54 (M + 1).

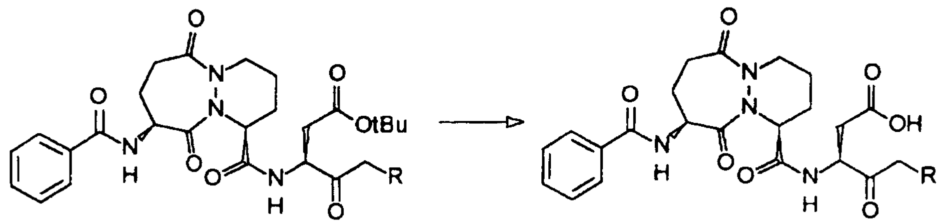
[3*S*(1*S*,9*S*)] 3-[9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-

Calcd for $C_{25}H_{27}N_5O_4S_2 \cdot H_2O$: C, 50.75; H, 4.94 N, 11.84. Found: C, 51.34; H, 4.70; N, 11.58. MS (ES^+) 572.

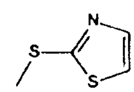
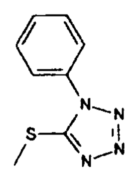
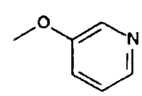
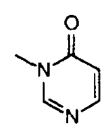
[3*S*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5-(1-phenyl-1H-tetrazole-5-thio) pentanoate (509b). **507a** (100mg, 0.17mmol) in dry dimethylformamide (1.5ml) was treated with 1-phenyl-1H-tetrazole-5-thiol (33mg, 0.187mmol) and potassium fluoride (15mg, 0.34mmol). The mixture was stirred at room temperature for 2h, diluted with ethyl acetate, washed with aqueous sodium bicarbonate (x2), brine, dried ($MgSO_4$) and evaporated. The product was purified by flash chromatography on silica gel eluting with ethyl acetate to give 103mg (88%) as a colourless foam: $[\alpha]_D^{23}$ -92.2° (c 0.1, CH_2Cl_2); IR (KBr) 3334, 1726, 1660, 1528, 1501, 1417, 1394, 1368, 1279, 1253, 1155; ^1H NMR ($CDCl_3$) δ 7.82 (2H, m), 7.60-7.40 (8H, m), 7.39 (1H, d, J = 8.1), 7.05 (1H, d, J = 7.3), 5.26 (1H, m), 5.15 (1H, m), 4.99 (1H, m), 4.60 (2H, m), 4.30 (1H, d, J = 17.2H), 3.32 (1H, m), 3.10-2.75 (4H, m), 2.40 (1H, m), 2.24 (1H, m), 1.90 (3H, m), 1.75 (1H, m), 1.44 (9H, s). MS (ES^+) 691.47 (M^+ + 1).

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxo-5(1-phenyl-1H-tetrazole-5-thio) pentanoic acid (280), was synthesized via method used to prepare **505** from **504**. **509b** (98mg, 0.142mmol) in dichloromethane (1ml) was cooled to 0° and trifluoroacetic acid (1ml) was added. The mixture was stirred at 0° for 15min and at

acid in acetic acid (1.84ml, 9.2mmol, 2.2equiv) at 0°C, under nitrogen. After 10min stirring at 0°C the reaction was complete and a white solid crystallised in the medium. The solid was filtered and washed with ethylacetate and diethylether to afford 2.20g (100%) of [3*S*(1*S*,9*S*)] 5-bromo-3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid which was used without further purification: ^1H NMR (D_6-DMSO) δ 8.87 (1H, d, J = 7.3), 8.63 (1H, d, J = 7.6), 7.91-7.87 (2H, m), 7.60-7.44 (3H, m), 6.92 (1H, bs), 5.14-5.09 (1H, m), 4.92-4.65 (2H, m), 4.43 (2H, AB), 4.41-4.35 (1H, m), 3.33-3.22 (1H, m), 2.98-2.90 (1H, m), 2.89-2.57 (2H, m), 2.35-2.15 (3H, m), 1.99-1.91 (2H, m), 1.75-1.60 (2H, m). A solution of the bromoketone (535mg, 1mmol) in dry DMF (10ml) was treated with potassium fluoride (150mg, 2.5mmol, 2.5 equiv), under nitrogen. After 5min stirring at room temperature, 2-mercaptothiazole (140mg, 1.2mmol, 1.2equiv) was added. After overnight reaction ethylacetate (150ml) was added and the organic solution was washed with brine, dried over magnesium sulphate and reduced in vacuo. The residue was crystallised in diethyl ether, filtered and purified on silica gel using a gradient of MeOH (0% to 5%) in dichloromethane. Evaporation afforded 344mg (60%) of a white solid: mp. 90-95°C (decomp.); $[\alpha]_D^{20}$ -82° (c 0.2, CH_2Cl_2); IR (KBr) 3328, 2941, 1745, 1659, 1535, 1422, 1276, 1255, 1223, 1072; ^1H NMR (D_6-DMSO) δ 8.92 (1H, d, J = 7.6), 8.68 (1H, d, J = 7.6), 7.98-7.90 (2H, m), 7.75-7.67 (1H, m), 7.64-7.50 (4H, m), 5.22-5.18 (1H, m), 4.95-4.74 (2H, m), 4.58-4.38 (3H, m), 3.52-3.19 (1H, m), 3.05-2.65 (4H, m), 2.40-1.50 (6H, m). Anal.



509a-d 510a, 280, 283, 510d

compound	R
509a 510a	
509b 280	
509c 283	
509d 510d	

[3*S*(1*S*,9*S*)] 3-(9-Benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-(2-mercaptothiazole)-4-oxopentanoic acid (510a). A solution of **506a** (2.27g, 4.2mmol) in dry dichloromethane (50ml) was treated with 30% hydrobromic

m). Anal. Calcd for $C_{24}H_{26}C_{12}N_4O_{10}\cdot H_2O$: C, 46.54; H, 4.56; N, 9.05. Found: C, 46.36; H, 4.14; N, 8.88.

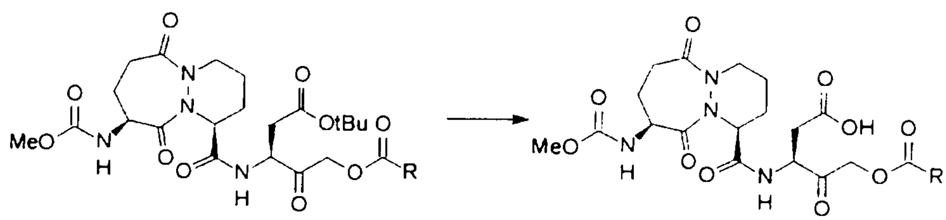
[3*S*(1*S*,9*S*)] t-Butyl 5-(2,6-dimethylbenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (508b), was synthesized by a similar method as compound **508a** to afford a pale yellow foam (460mg, 82%): $[\alpha]_D^{22}$ -115° (c 0.20, CH_2Cl_2); IR (KBr) 3413, 2960, 1729, 1675, 1528, 1514, 1461, 1421, 1368, 1265, 1116, 1096; ^{1}H NMR ($CDCl_3$) δ 7.27-7.03 (4H, m), 5.48 (1H, d, J = 8.2), 5.20-5.14 (1H, m), 5.04 (2H, AB), 4.93-4.86 (1H, m), 4.80-4.56 (2H, m), 3.77 (3H, s), 3.32-3.15 (1H, m), 3.00-2.56 (4H, m), 2.37 (6H, s), 2.19-1.77 (5H, m), 1.45 (9H, s), 2.41-2.25 (1H, m). MS (ES^+) 617.

[3*S*(1*S*,9*S*)] 5-(2,6-Dimethylbenzoyloxy)3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (285), was synthesized by a similar method as compound **284** to afford a white solid (303mg, 78%): mp. 110°C (decomp.); $[\alpha]_D^{20}$ -128° (c 0.10, CH_2Cl_2); IR (KBr) 3339, 2958, 1731, 1666, 1529, 1420, 1266, 1248, 1115, 1070; ^{1}H NMR (D_6-DMSO) δ 8.90 (1H, d, J = 7.4), 7.54 (1H, d, J = 7.9), 7.36-7.28 (1H, m), 7.17-7.14 (2H, m), 5.19-5.15 (3H, m), 4.84-4.74 (1H, m), 4.45-4.37 (2H, m), 3.59 (3H, s), 3.45-3.25 (1H, m), 2.95-2.64 (4H, m), 2.35 (6H, s), 2.30-1.60 (6H, m). Anal. Calcd for $C_{26}H_{32}N_4O_{10}\cdot H_2O$: C, 53.98; H, 5.92; N, 9.68. Found: C, 53.50; H, 5.52; N, 9.49. MS (ES^+) 559.

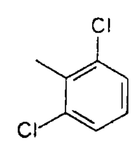
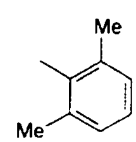
506c (547mg, 1mmol) in DMF (4ml) was added potassium fluoride (145mg, 2.5mmol, 2.5 equiv). After 10min stirring at room temperature, 2,6-dichlorobenzoic acid (229mg, 1.2mmol, 1.2 equiv) was added. After 3h reaction at room temperature, ethyl acetate (30ml) was added. The solution was washed with a saturated solution of sodium bicarbonate (30ml), brine, dried over $MgSO_4$ and concentrated in vacuo to afford 590mg (90%) of a pale yellow foam: $[\alpha]_D^{22}$ -85° (c 0.20, CH_2Cl_2); IR (KBr) 3400, 2956, 1737, 1675, 1528, 1434, 1414, 1368, 1344, 1272, 1197, 1152, 1061; ^{1}H NMR ($CDCl_3$) δ 7.36-7.33 (3H, m), 7.04 (1H, d, J = 8.0), 5.46 (1H, d, J = 7.8), 5.19-5.16 (1H, m), 5.08 (2H, AB), 4.97 - 4.55 (1H, m), 4.69-4.55 (2H, m), 3.68 (3H, s), 3.30-3.10 (1H, m), 3.01-2.50 (4H, m), 2.40-2.33 (1H, m), 2.15-1.60 (5H, m), 1.44 (9H, s). Anal. Calcd for $C_{28}H_{34}Cl_2N_4O_{10}$: C, 51.15; H, 5.21; N, 8.52. Found: C, 51.35; H, 5.32; N, 8.56.

[3*S*(1*S*,9*S*)] 5-(2,6-Dichlorobenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoic acid (284), was synthesized from **508a** via method used to prepare **505** from **504** which afforded 330mg (65%) of a white solid: mp. 115°C (decomp.); $[\alpha]_D^{20}$ -107° (c 0.2, CH_2Cl_2); IR (KBr) 3340, 2954, 1736, 1664, 1530, 1434, 1272, 1198, 1148, 1060; ^{1}H NMR (D_6-DMSO) δ 8.91 (1H, d, J = 7.2H), 7.67-7.63 (3H, m), 7.54 (1H, d, J = 8.0), 5.24 (2H, s), 5.20-5.15 (1H, m), 4.79-4.70 (1H, m), 4.46-4.37 (2H, m), 3.58 (3H, s), 3.33-3.20 (1H, m), 2.94-2.55 (4H, m), 2.30-1.60 (6H,

method as compound **507a** to afford a pale yellow foam (84%): $[\alpha]_D^{22}$ -109.6° (c 0.1, CH_2Cl_2); IR (KBr) 3324, 1727, 1659, 1535, 1458, 1444, 1423, 1369, 1279, 1256, 1223, 1155; ^{1}H NMR ($CDCl_3$) δ 7.12 (1H, d, J = 7.8), 6.33 (1H, d, J = 7.5), 5.19 (1H, m,), 4.97 (2H, m), 4.58 (1H, m), 4.06 (2H, s), 3.20 (1H, m), 3.05-2.69 (4H, m), 2.35 (1H, m), 2.14-1.68 (5H, m), 2.03 (3H, s), 1.44 (9H, s). Anal. Calcd for $C_{21}H_{31}BrN_4O_7 \cdot 0.3H_2O$: C, 46.99; H, 5.93; N, 10.44. Found: C, 46.97; H, 5.90; N, 10.35.



508a, b **284, 285**

compound	R
508a **284**	
508b **285**	

[3S(1S,9S)] t-Butyl 5-(2,6-dichlorobenzoyloxy)-3-[6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxobutanoate (508a). To a solution of

[3*S*(1*S*,9*S*)] t-Butyl 5-bromo-3-(6,10-dioxo-9-methanesulphonamido-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507b), was prepared by a similar method as compound **507a**. (68%) as an orange foam: $[\alpha]_D^{20}$ -135° (c 0.053, CH_2Cl_2); IR (KBr) 3429, 2944, 2935, 1723, 1670, 1458, 1408, 1327, 1225, 1154, 991; ^1H NMR ($CDCl_3$) δ 7.38 (1H, d, J = 8.2), 5.69 (1H, d, J = 9.3), 5,43-5.34 (1H, m), 5.07-4.97 (1H, m), 4.70-4.42 (2H, m), 4.12 (2H, s), 3.35-3.17 (1H, m), 3.10-2.69 (4H, m), 2.98 (3H, s), 2.43-2.33 (1H, m), 2.15-1.65 (5H, m), 1.43 (9H, s). Anal. Calcd for $C_{20}H_{31}BrN_4O_8S$: C, 42.33; H, 5.51; N, 9.87. Found: C, 42.69; H, 5.52; N, 9.97.

[3*S*(1*S*,9*S*)] t-Butyl 5-bromo-3-(6,10-dioxo-9-(methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507c), was prepared by a similar method as compound **507a** to afford a pale yellow foam (320mg, 78%): $[\alpha]_D^{20}$ -107° (c 0.2, CH_2Cl_2); IR (KBr) 3401, 2956, 1726, 1670, 1528, 1452, 1415, 1395, 1368, 1276, 1251, 1155, 1064; ^1H NMR ($CDCl_3$) δ 7.07 (1H, d, J = 7.6), 5.47 (1H, d, J = 8.1), 5.21-5.16 (1H, m), 5.03-4.94 (1H, m), 4.75-4.56 (2H, m), 4.06 (2H, s), 3.69 (3H, s), 3.31-3.13 (1H, m), 3.03-2.92 (2H, m), 2.81-2.58 (2H, m), 2.41-2.31 (1H, m), 2.10-1.66 (5H, m), 1.44 (9H, s).

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-acetylamino-6,10-dioxo—1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-bromo-4-oxopentanoate (507g), was prepared by a similar

method as compound **506a**. 81%: $[\alpha]_D^{28}$ -146.7° (c 0.4, CH_2Cl_2); IR (KBr) 3438, 2904, 2113, 1728, 1669, 1523, 1368, 1328, 1155; ^1H NMR ($CDCl_3$) δ 7.32 (1H, d), 6.43 (1H, d), 5.50 (1H, s), 5.22 (1H, m), 4.94 (1H, m), 4.77 (1H, m), 4.60 (1H, m), 3.24 (1H, m), 3.03-2.52 (4H, m), 2.36 (1H, m), 2.10-1.64 (5H, m), 2.02 (3H, s), 1.45 (9H, s). Anal. Calcd for $C_{21}H_{20}N_6O_7$: C, 52.69; H, 6.32; N, 17.05. Found: C, 52.51; H, 6.27; N, 17.36. MS (ES^+) 477(M^+ - 1, 100%).

[3*S*(1*S*,9*S*)] t-Butyl 5-bromo-3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (507a). **506a** (3.0g, 5.55mmol) in dry dichloromethane (40ml) was cooled to 0° and 30% hydrobromic acid in acetic acid (1.1ml, 5.55mmol) was added dropwise over 4min. The mixture was stirred at 0° for 9min and quenched with aqueous sodium bicarbonate. The product was extracted into ethyl acetate, washed with aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and evaporated to give 2.97g (92%) of a colourless foam: $[\alpha]_D^{23}$ -82.3° (c 0.23, CH_2Cl_2); IR (KBr) 3333, 1726, 1659, 1530, 1458, 1447, 1422, 1395, 1368, 1279, 1256, 1222, 1155, 728; ^1H NMR ($CDCl_3$) δ 7.81 (2H, m), 7.50 (3H, m), 7.11 (1H, d, J = 8.0), 7.01 (1H, d, J = 7.4), 5.20 (2H, m), 5.00 (1H, m), 4.06 (2H, s), 3.28 (1H, m), 3.20-2.70 (4H, m), 2.42 (1H, m), 2.10-1.85 (4H, m), 1.72 (1H, m), 1.44 (9H, s). Anal. Calcd for $C_{26}H_{33}N_4O_7Br \cdot 0.7H_2O$: C, 51.53; H, 5.72 N, 9.24. Found: C, 51.55; H, 5.52; N, 9.09. MS (ES^+) 595, 593 (M^+ + 1).

1.85 (4H, m), 1.70 (1H, m), 1.45 (9H, s). MS (ES^+) 539.58 (M - 1, 97.9%) 529.59 (100).

[3*S*(1*S*,9*S*)] t-Butyl 5-diazo-3-[6,10-dioxo-(9-methanesulphonamido)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (506b), was prepared by a similar method as compound **506a**. 74% as yellow orange solid: mp. 75°C (decomp.); $[\alpha]_D^{20}$ -92.0° (c 0.036, CH_2Cl_2); IR (KBr) 3438, 2904, 2113, 1728, 1669, 1523, 1368, 1328, 1155; ^1H NMR ($CDCl_3$) δ 7.48 (1H, d, J = 8.1), 5.83-5.68 (1H, m,), 5.55-5.50 (1H, m), 5.43-5.14 (1H, m), 4.83-4.45 (3H, m), 3.40-3.19 (1H, m), 2.98 (3H, s), 2.92-2.30 (4H, m), 2.24-1.70 (6H, m), 1.43 (9H, s).

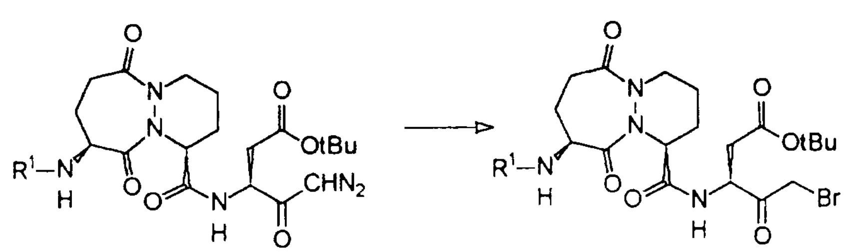
[3*S*(1*S*,9*S*)] t-Butyl 5-diazo-3-[6,10-dioxo-(9-methoxycarbonyl)amino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxopentanoate (506c), was prepared by a similar method as compound **506a** to afford a pale yellow foam (405mg, 82%): $[\alpha]_D^{20}$ -144° (c 0.2, CH_2Cl_2); IR (KBr) 3339, 2978, 2958, 2112, 1728, 1674, 1530, 1459, 1415, 1367, 1274, 1252, 1154, 1063; ^1H NMR ($CDCl_3$) δ 7.23 (1H, d, J = 8.2), 5.51-5.31 (2H, m), 5.21-5.16 (1H, m), 4.77-4.55 (3H, m), 3.68 (3H, s), 3.35-3.18 (1H, m), 3.04-2.51 (4H, m), 2.40-2.30 (1H, m), 2.09-1.66 (5H, m), 1.45 (9H,s). MS (ES^+) 493.

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-acetylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-diazo-4-oxopentanoate (506g), was prepared by a similar

compound	R^1
506a **507a**	PhC(O)-
506b **507b**	$MeS(O)_2$-
506c **507c**	MeOC(O)-
506g **507g**	$CH_3C(O)$-

[3*S*(1*S*,9*S*)] t-Butyl 3-(9-benzoylamino-6,10-dioxo-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-5-diazo-4-oxopentanoate (506a). A solution of **212e** (321mg, 0.929mmol) and (3*S*) t-butyl 3-amino-5-diazo-4-oxopentanoate (198mg, 0.929mmol) in dichloromethane (3ml) was cooled to 0° and N,N-diisopropylethylamine (0.16ml, 1.86mmol) and [2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium tetrafluoroborate (328mg, 1.02mmol) were added. The solution was stirred overnight at room temperature, diluted with ethyl acetate and washed with 1M $NaHSO_4$ (x2), aqueous $NaHCO_3$ (x2), brine, dried over magnesium sulphate and evaporated. Chromatography on silica gel eluting with ethyl acetate gave **506a** (425mg, 85%) as a colourless foam: $[\alpha]_D^{23}$ -124.9° (c 0.2, CH_2Cl_2); IR (KBr) 3332, 2111, 1728, 1658, 1532, 1421, 1392, 1367, 1279, 1256, 1155; ^1H NMR ($CDCl_3$) δ 7.82 (2H, m), 7.49 (3H, m), 7.28 (1H, d, J = 9.3), 7.05 (1H, d, J = 7.3), 5.06 (1H, s), 5.18 (2H, m), 4.78 (1H, m), 4.62 (1H, m), 3.29 (1H, m), 3.08-2.79 (3H, m), 2.58 (1H, dd, J = 16.8, 5.6), 2.20-

[3*S*(1*S*,9*S*)] 5-(3-Chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoic acid (505e). A solution of **217** (0.33g, 0.51mmol) in dry dichloromethane (3ml) was cooled (ice/water) with protection from moisture. Trifluoroacetic acid (2ml) was added with stirring. The solution was kept at room temperature for 2h after removal of the cooling bath, then concentrated in vacuo. The residue was evaporated three times from dichloromethane, triturated with diethyl ether and filtered. The solid was purified by flash chromatography (silica gel, 0-6% methanol in dichloromethane) to give the product as a white glassy solid (0.296g, 98%): mp 110-122°C; $[\alpha]_D^{22}$ -163.5° (c 0.1, CH_3OH); IR (KBr) 3514-3337, 1726, 1664, 1513, 1420, 1245, 1152, 1134, 990; ^1H NMR (CD_3OD) δ 7.79 (1H, d, J = 5.2), 7.12 (1H, d, J = 5.2), 5.20 (1H, m), 5.02-4.72 (2H, m, masked by H_2O), 4.59-4.32 (3H, m), 3.48-3.29, 3.08-2.75, 2.50-2.41, 2.31-2.22, 2.08-1.89, 1.72-1.63 (11H, 6m), 2.95 (3H, s).



506a-c,g 507a-c,g

2.19-2.06 (2H, m), 2.02-1.79 (3H, m), 1.63-1.52 (1H, m). Anal. Calcd for $C_{29}H_{32}N_4O_{11}S \cdot 0.5H_2O$: C, 53.29; H, 5.09; N, 8.57; S, 4.90. Found: C, 53.24; H, 5.14; N, 8.34; S, 4.86. MS (ES^+) 643 (M - 1, 100%), 385 (62).

[3*S*,4*R*(1*S*,9*S*)] t-Butyl 5-(3-chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-hydroxypentanoate (503e), was prepared by a similar method to that described for compound **213e**, to afford an off white solid (70%): mp. 100-103°C; $[\alpha]_D^{25}$ -84.0° (c 0.05, CH_2Cl_2); IR (KBr) 3459-3359, 1722, 1664, 1514, 1368, 1328, 1278, 1247, 1155; ^1H NMR ($CDCl_3$) δ 7.52 (1H, m), 7.06-6.99 (2H, m), 5.69 (1H, d, J = 9.0), 5.23 (1H, m), 4.61-4.16 (6H, m), 3.36-3.19 (1H, m), 2.96 (3H, s), 2.67-2.49, 2.42-2.32, 2.06-1.89, 1.69 (10H, 4m), 1.43 (9H, s).

[3*S*(1*S*,9*S*)] t-Butyl 5-(3-chlorothien-2-oyloxy)-3-(6,10-dioxo-9-methanesulphonylamino-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido)-4-oxopentanoate (504e), was prepared by a similar method to that described for compound **216e**, to afford a white solid (98%): mp. 91-98°C; $[\alpha]_D^{25}$ -112.5°C (c 0.06, CH_2Cl_2); IR (KBr) 3453-3364, 1727, 1668, 1513, 1420, 1368, 1245, 1155; ^1H NMR ($CDCl_3$) δ 7.54 (1H, d, J = 5.3), 7.18 (1H, d, J = 7.18), 7.05 (1H, d, J = 5.4), 5.42 (1H, d, J = 8.9), 5.25 (1H, m), 5.02 (2H, m), 4.96-4.87 (1H, m), 4.65-4.42 (2H, m), 3.34-3.17 (1H, m), 2.97-2.93 (1H, m), 2.97 (3H, s), 2.87-2.78, 2.73-2.50, 2.38-2.32, 2.13-1.88, 1.69-1.60 (9H, 5m), 1.44 (9H, s).

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-phenoxybenzoyloxy) pentanoate (504d), was synthesized by a similar method as compound **216e** to afford a colourless powder (466mg, 85%): mp. 75-100°C; $[\alpha]_D^{22}$ -99.3° (c 0.60, CH_2Cl_2); IR (KBr) 3335, 2978, 2937, 1728, 1669, 1584, 1525, 1487, 1444, 1416, 1369, 1328, 1272, 1227, 1188, 1155, 989, 754; ^{1}H NMR ($CDCl_3$) δ 7.82-7.77 (1H, m), 7.66-7.65 (1H, m), 7.46-7.32 (4H, m), 7.26-7.10 (2H, m), 7.04-6.98 (2H, m), 5.68 (1H, d), 5.37-5.31 (1H, m), 5.11 (1H, d), 5.02-4.88 (2H, m), 4.66-4.42 (2H, m), 3.35-3.17 (1H, m), 2.98-2.89 (1H, m), 2.96 (3H, s), 2.84-2.78 (1H, m), 2.72-2.47 (1H, m), 2.42-2.32 (1H, m), 2.14-1.58 (6H, m), 1.43 (9H. s). Anal. Calcd for $C_{33}H_{40}N_4O_{11}S$: C, 56.56; H, 5.75; N, 8.00. Found: C, 56.36; H, 5.82; N, 7.71. MS (ES^+) 723 (56%), 718 (90), 701 (M^+ + 1, 36), 645 (100).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(3-phenoxybenzoyloxy)pentanoic acid (505d), was synthesized by a similar method as compound **217** to afford a colourless foam (353mg, 73%): mp. 80-115°C; $[\alpha]_D^{23}$ -138° (c 0.11, MeOH); IR (KBr) 3327, 2937, 1728, 1666, 1584, 1529, 1487, 1443, 1413, 1328, 1273, 1227, 1189, 1155, 1134, 989, 754; ^{1}H NMR (D_6-DMSO) δ 8.82 (1H, d), 7.76-7.72 (1H, m), 7.61-7.53 (2H, m), 7.48-7.32 (4H, m), 7.24-7.17 (1H, m), 7.11-7.06 (2H, m), 5.14-5.06 (3H, m), 4.73-4.64 (1H, m), 4.38-4.24 (2H, m), 2.92 (3H, s), 2.89-2.61 (3H, m), 2.38-2.27 (1H, m),

(2-phenoxybenzoyloxy)pentanoic acid (505c), was synthesized by a similar method as compound **217** to afford a colourless foam (252mg, 72%): mp. 90-125°C; $[\alpha]_D^{23}$ -133° (c 0.11, MeOH); IR (KBr) 3314, 2938, 1792, 1734, 1663, 1604, 1535, 1483, 1448, 1415, 1250, 1132, 756; ^{1}H NMR (D_6-DMSO) δ 8.81-8.76 (1H, m), 7.92 (1H, d), 7.68-7.54 (2H, m), 7.41-7.25 (3H, m), 7.16-6.91 (4H, m), 5.13-4.98 (2H, m), 4.72-4.63 (1H, m), 4.37-4.21 (2H, m), 2.92 (3H, s), 2.90-2.60 (3H, m), 2.35-2.26 (1H, m), 2.17-2.05 (2H, m), 1.99-1.80 (2H, m), 1.61-1.50 (1H, m).Anal. Calcd for $C_{29}H_{32}N_4O_{11}S \cdot 0.5H_2O$: C, 53.29; H, 5.09; N, 8.57; S, 4.90. Found: C, 53.57; H, 5.18; N, 8.32; S, 4.75. MS (ES^+) 643 (M - 1, 100%).

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-hydroxy-5-(3-phenoxybenzoyloxy) pentanoate (503d), was synthesized by a similar method as compound **213e** to afford a colourless solid (563mg, 90%): IR (KBr) 3349, 2978, 2935, 1724, 1664, 1583, 1536, 1489, 1443, 1370, 1327, 1271, 1226, 1189, 1155, 1073, 990, 755; ^{1}H NMR ($CDCl_3$) δ 7.77 (1H, d), 7.67 (1H, m), 7.45-7.10 (6H, m), 7.00 (2H, d), 5.93-5.80 (1H, m), 5.36-5.30 (1H, m), 4.63-4.24 (5H, m), 4.15-4.09 (1H, m), 3.37-3.22 (1H, m), 2.98-2.74 (1H, m), 2.94 (3H, s), 2.70-2.47 (3H, m), 2.40-2.30 (1H, m), 2.15-1.60 (5H, m), 1.42 (9H, s). Anal. Calcd for $C_{33}H_{42}N_4O_{11}S \cdot H_2O$: C, 54.99; H, 6.15; N, 7.77; S, 4.45. Found: C, 54.60; H, 5.88; N, 7.49; S, 4.50. MS (ES^+) 725 (19%), 720 (91), 703 (M^+ + 1, 74), 647 (76), 629 (100), 433 (78).

(1H, m), 7.39-7.18 (3H, m), 7.14-7.07 (1H, m), 7.00-6.90 (3H, m), 6.75 (1H, d), 5.57-5.50 (1H, m), 5.21-5.09 (1H, m), 4.64-4.42 (2H, m), 4.36-4.12 (3H, m), 3.95-3.87 (1H, m), 3.39-3.18 (1H, m), 3.00-2.82 (1H, m), 2.95 (3H, s), 2.69-2.48 (3H, m), 2.42-2.28 (1H, m), 2.07-1.62 (6H, m), 1.42 (9H, s). Anal. Calcd for $C_{33}H_{42}N_4O_{11}S \cdot H_2O$: C, 54.99; H, 6.15; N, 7.77; S, 4.45. Found: C, 54.95; H, 5.95; N, 7.34; S, 4.20. MS (ES^+) 725 (26%), 720 (47), 703 (M^+ + 1, 34), 433 (100), 403 (89).

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-(2-phenoxybenzoyloxy) pentanoate (504c), was synthesized by a similar method as compound **216e** to afford a colourless powder: mp. 85-100°C; $[\alpha]_D^{22}$ -91.3° (c 0.52, CH_2Cl_2); IR (KBr) 3328, 2978, 2935, 1732, 1669, 1603, 1524, 1483, 1450, 1396, 1369, 1296, 1276, 1237, 1155, 1132, 1082, 989, 755; ^1H NMR ($CDCl_3$) δ 8.03-7.98 (1H, m), 7.52-7.44 (1H, m), 7.37-7.07 (5H, m), 7.01-6.92 (3H, m), 5.52 (1H, d), 5.28-5.20 (1H, m), 5.06-4.84 (3H, m), 4.64-4.39 (2H, m), 3.32-3.14 (1H, m), 2.99-2.88 (1H, m), 2.94 (3H, s), 2.65-2.45 (2H, m), 2.39-2.29 (1H, m), 2.12-1.58 (6H, m), 1.40 (9H, s). Anal. Calcd for $C_{33}H_{40}N_4O_{11}S$: C, 56.56; H, 5.75; N, 8.00; S, 4.58. Found: C, 56.37; H, 5.84; N, 7.69; S, 4.37. MS (ES^+) 723 (30%), 718 (100), 701 (M^+ + 1, 23), 645 (59).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-oxo-5-

MS (ES^+) 712 (31%), 707 (100), 690 (M^+ + 1, 41), 634 (55).

[3*S*(1*S*,9*S*)] 3-[6,10-Dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(5-methyl-3-phenylisoxazoyloxy)-4-oxopentanoic acid (505b), was synthesized by a similar method as compound **217** to afford a colourless powder (499mg, 96%): mp. 95-145°C; $[\alpha]_D^{22}$ -137° (c 0.12, MeOH); IR (KBr) 3323, 2936, 1732, 1665, 1529, 1452, 1421, 1312, 1275, 1256, 1221, 1183, 1153, 1135, 1101, 990; ^{1}H NMR (CD_3OD) δ 7.67-7.56 (2H, m), 7.49-7.38 (4H, m), 5.23-5.12 (1H, m), 5.02 (1H, d), 4.79-4.73 (1H, m), 4.52-4.34 (3H, m), 3.48-3.25 (2H, m), 3.03-2.85 (2H, m), 2.94 (3H, s), 2.74 (3H, s), 2.79-2.66 (1H, m), 2.52-2.38 (1H, m), 2.29-2.14 (1H, m), 2.04-1.70 (4H, m). Anal. Calcd for $C_{27}H_{31}N_5O_{11}S \cdot H_2O$: C, 49.77; H, 5.18; N, 10.75; S, 4.92. Found: C, 49.83; H, 5.01; N, 10.27; S, 4.84. MS (ES^+) 746 (42%), 632 (M - 1, 100), 386 (60). Accurate mass calculated for $C_{27}H_{32}N_5O_{11}S$ (MH^+): 634.1819. Found: 634.1807.

[3*S*,4*RS*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-4-hydroxy-5-(2-phenoxybenzoyloxy)pentanoate (503c), was synthesized by a similar method as compound **213e** to afford a colourless solid (446mg, 84%): IR (KBr) 3345, 2976, 2935, 1727, 1664, 1603, 1535, 1483, 1451, 1416, 1395, 1369, 1328, 1297, 1277, 1237, 1155, 1135, 1076, 990, 755; ^{1}H NMR ($CDCl_3$) δ 7.98-7.89 (1H, m), 7.55-7.45

(methanesulphonylamino)-1-carboxamido]-4-hydroxy-5-(5-methyl-3-phenylisoxazoyloxy)pentanoate (503b), was synthesized by a similar method as compound **213e**, to afford an off-white powder (671mg, 88%): mp. 90-120°C; IR (KBr) 3345, 2977, 1727, 1664, 1532, 1450, 1423, 1369, 1323, 1310, 1276, 1257, 1154, 1101, 990, 766; ^{1}H NMR ($CDCl_3$) δ 7.61-7.55 (2H, m), 7.51-7.42 (3H, m), 6.86 (1H, d), 5.69 (1H, d), 5.21 (1H, m), 4.64-4.38 (2H, m), 4.15-4.05 (3H, m), 3.84 (1H, s), 3.31-3.14 (2H, m), 2.97-2.87 (1H, m), 2.94 (3H, s), 2.76 (3H, s), 2.64-2.48 (3H, m), 2.39-2.29 (1H, m), 2.04-1.61 (5H, m). Anal. Calcd for $C_{31}H_{41}N_5O_{11}S \cdot H_2O$: C, 52.46; H, 6.11; N, 9.87; S, 4.52. Found: C, 52.34; H, 5.92; N, 9.56; S, 4.44. MS (ES$^+$) 714 (47%), 692 (M$^+$ + 1, 84), 636 (100).

[3*S*(1*S*,9*S*)] t-Butyl 3-[6,10-dioxo-9-(methanesulphonylamino)-1,2,3,4,7,8,9,10-octahydro-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxamido]-5-(5-methyl-3-phenylisoxazoyloxy)-4-oxopentanoate (504b), was synthesized by a similar method as compound **216b** to afford a colourless powder (601mg, 93%): mp. 75-115°C; $[\alpha]_D^{23}$ -104° (c 0.26, CH_2Cl_2); IR (KBr) 3324, 2977, 2935, 1730, 1670, 1525, 1452, 1422, 1369, 1317, 1276, 1256, 1222, 1155, 1107, 990, 766; ^{1}H NMR ($CDCl_3$) δ 7.68-7.61 (2H, m), 7.47-7.38 (3H, m), 7.32-7.24 (1H, m), 5.56 (1H, d), 5.36-5.24 (1H, m), 5.04 (1H, d), 4.88 (1H, d), 4.86-4.77 (1H, m), 4.64-4.39 (2H, m), 3.32-3.17 (1H, m), 2.97-2.85 (1H, m), 2.93 (3H, s), 2.76 (3H, s), 2.80-2.71 (1H, m), 2.65-2.49 (1H, m), 2.41-2.30 (1H, m), 2.12-1.61 (6H, m), 1.42 (9H, s). Anal. Calcd for $C_{31}H_{39}N_5O_{11}S \cdot H_2O$: C, 52.61; H, 5.84; N, 9.90; S, 4.53. Found: C, 52.94; H, 5.69; N, 9.72; S, 4.51.

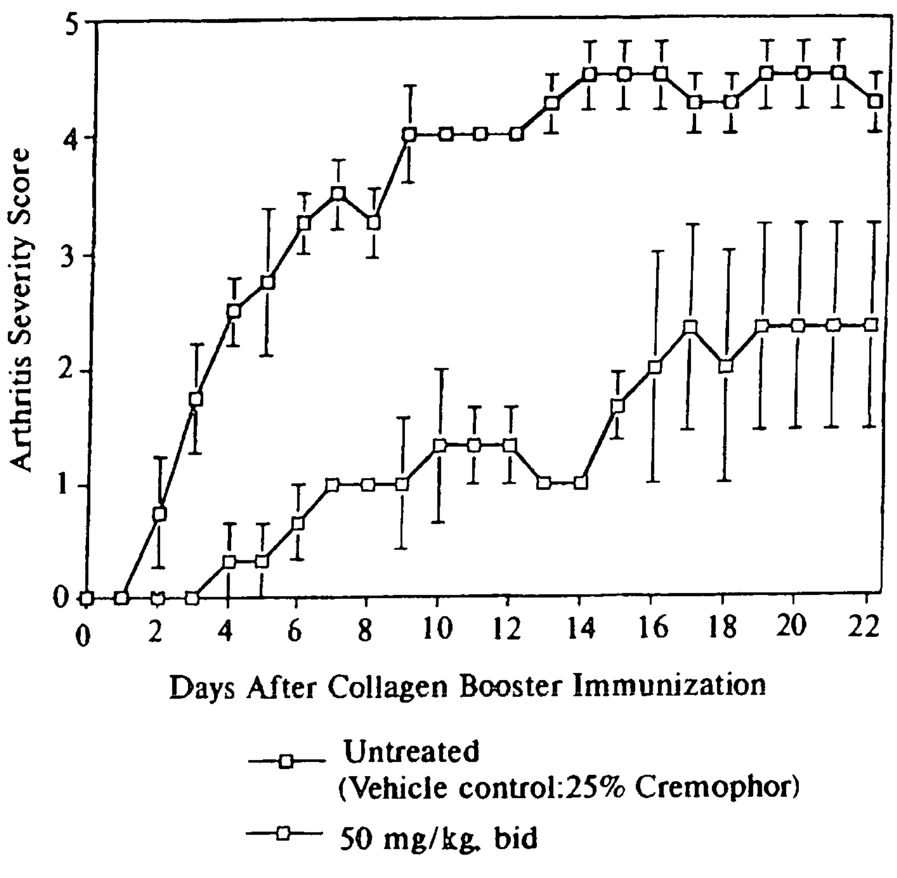

Arthritis Severity Score
0
1
2
3
4
5
0
2
4
6
8
10
12
14
16
18
20
22
Days After Collagen Booster Immunization
Untreated
(Vehicle control:25% Cremophor)
50 mg/kg. bid

FIG. 14

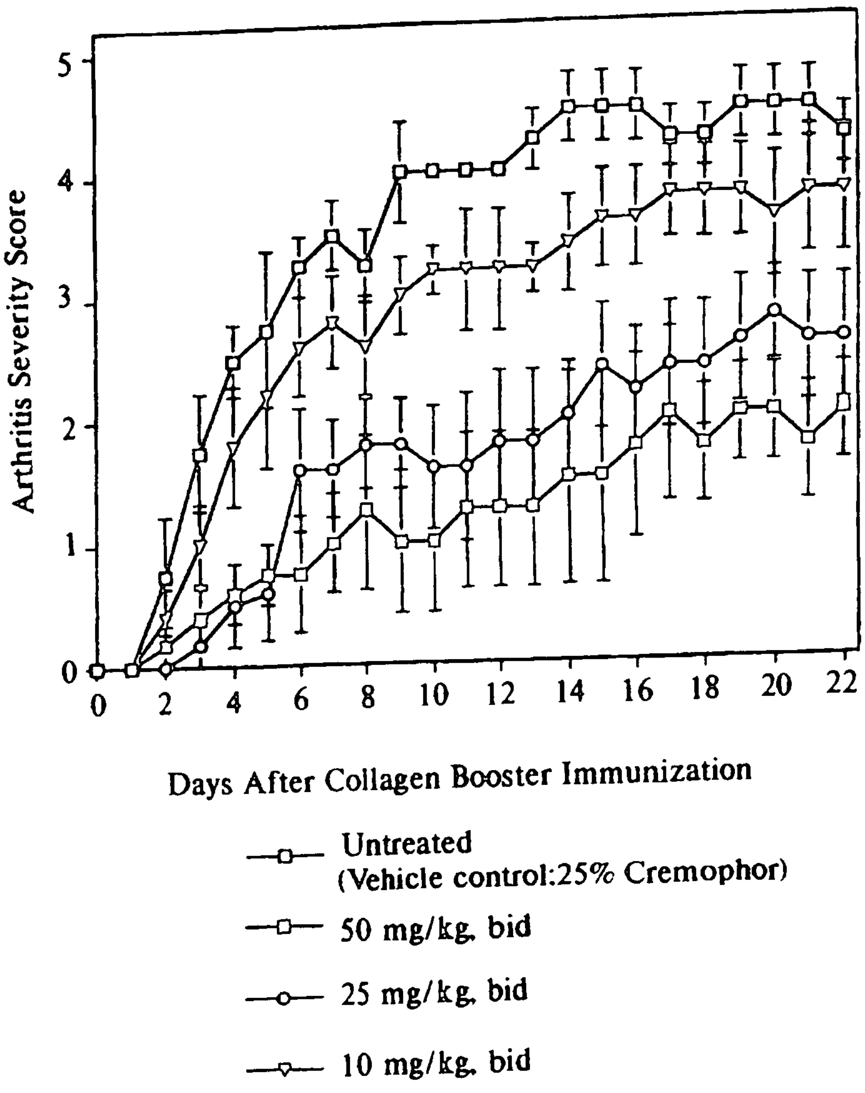

Arthritis Severity Score
5
4
3
2
1
0
0
2
4
6
8
10
12
14
16
18
20
22
Days After Collagen Booster Immunization
Untreated
(Vehicle control:25% Cremophor)
50 mg/kg, bid
25 mg/kg, bid
10 mg/kg, bid

FIG. 13

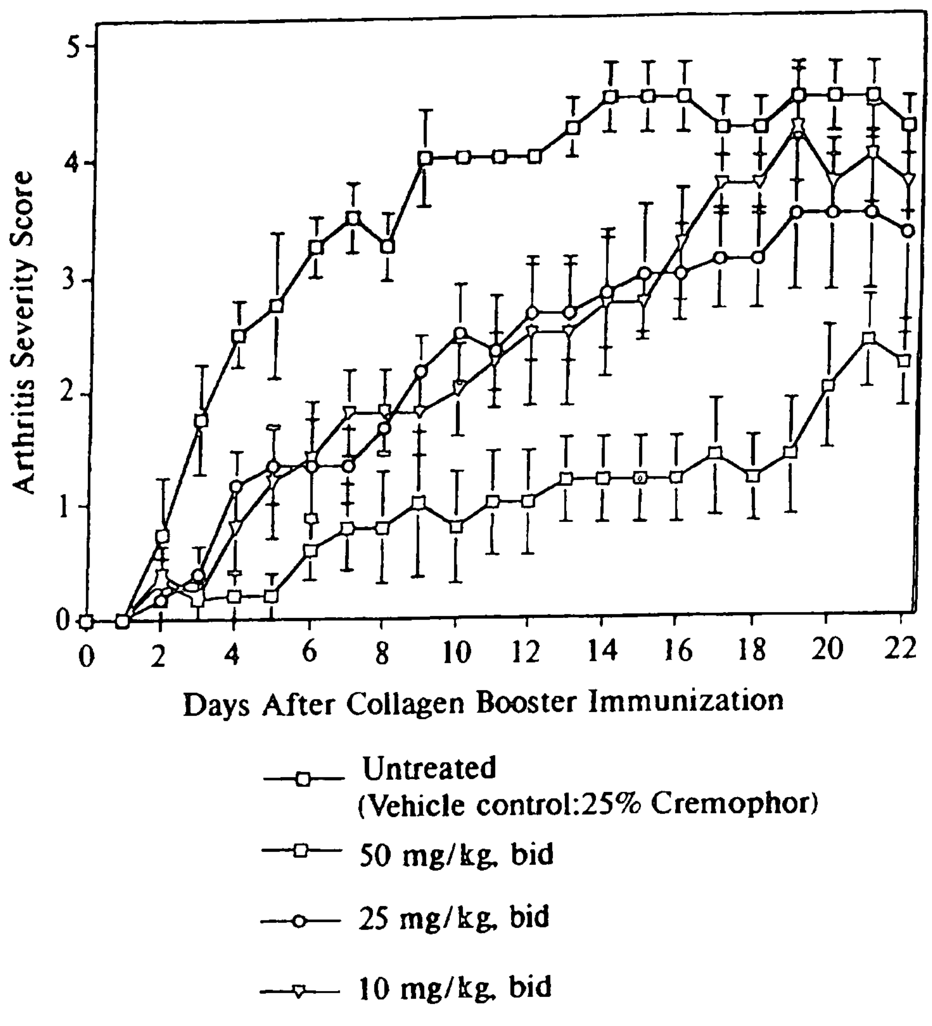

Arthritis Severity Score
0
1
2
3
4
5
0
2
4
6
8
10
12
14
16
18
20
22
Days After Collagen Booster Immunization
Untreated
(Vehicle control:25% Cremophor)
50 mg/kg, bid
25 mg/kg, bid
10 mg/kg, bid

FIG. 12

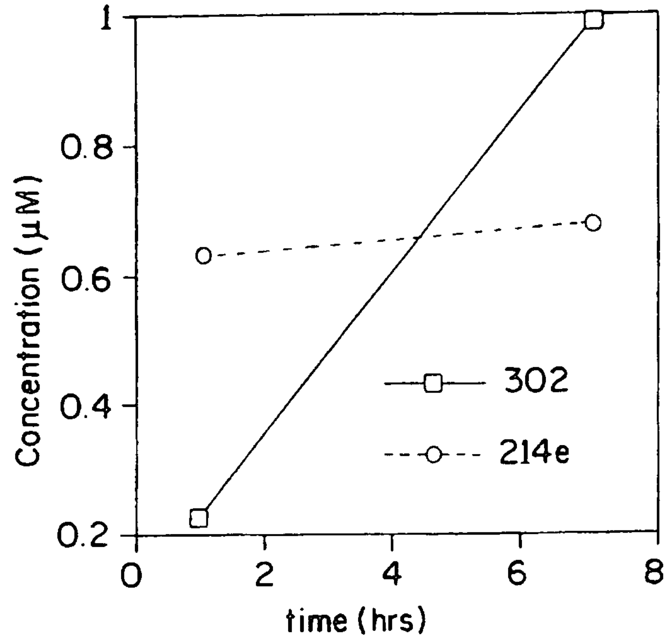


FIG. 11A

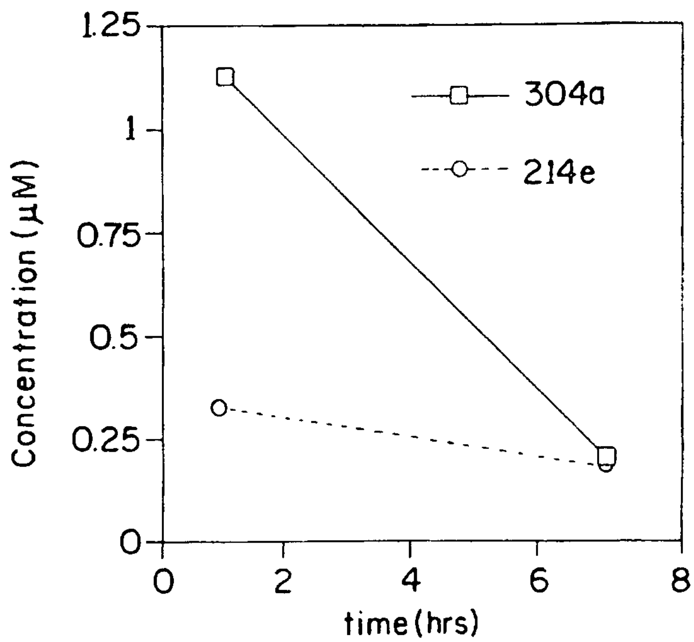


FIG. 11B

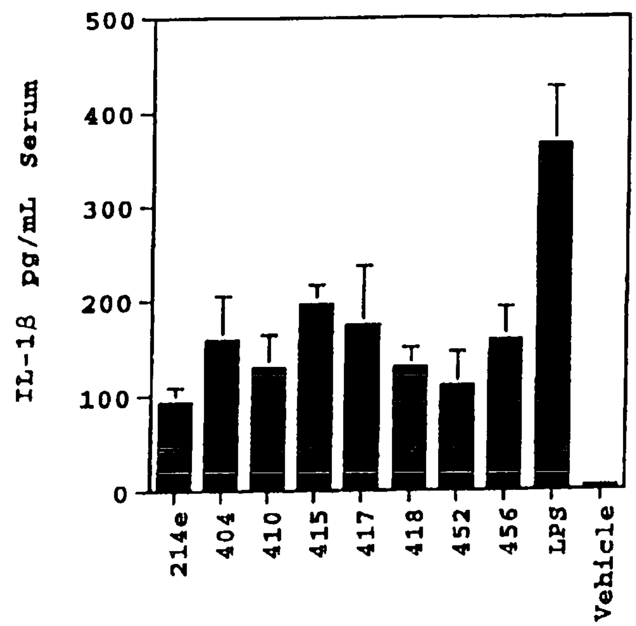
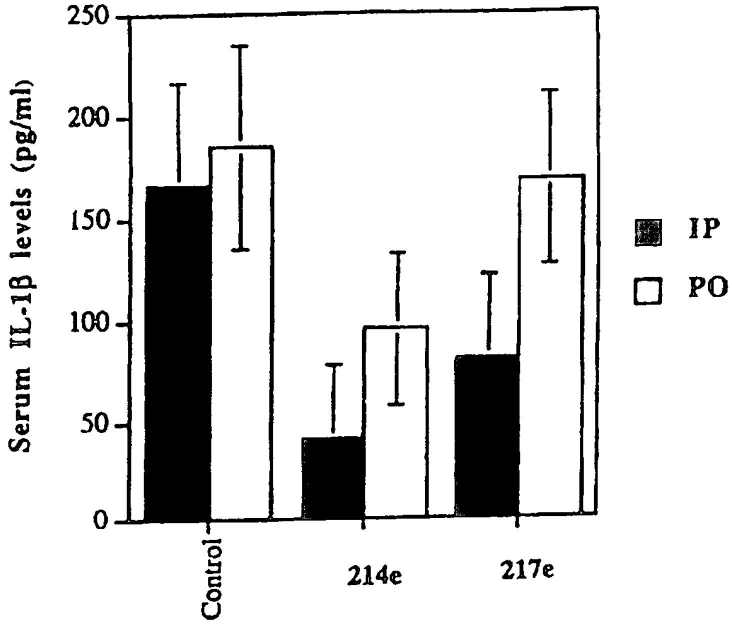
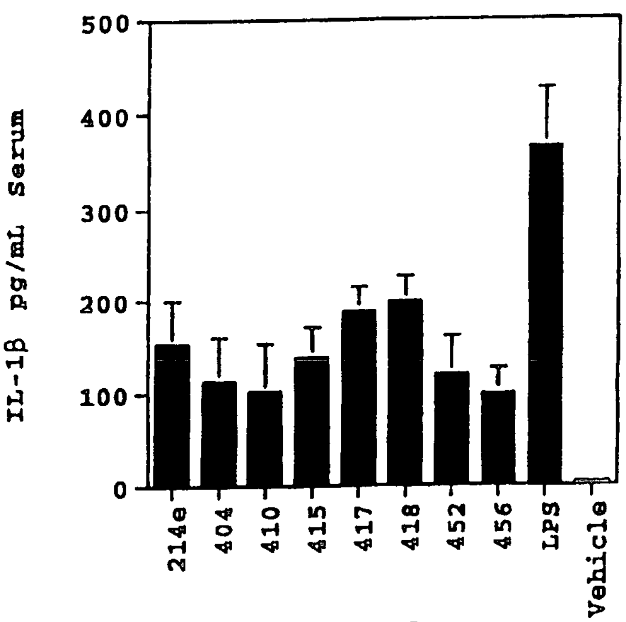

500
400
300
200
100
0
IL-1β pg/mL Serum
214e
404
410
415
417
418
452
456
LPS
Vehicle

FIG. 10



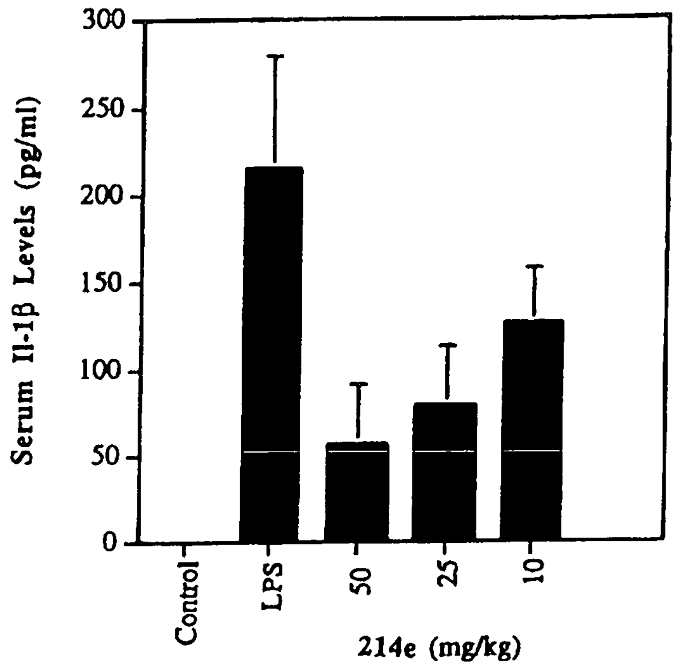
250
200
150
100
50
0
Serum IL-1β levels (pg/ml)
Control
214e
217e
IP
PO

FIG. 8



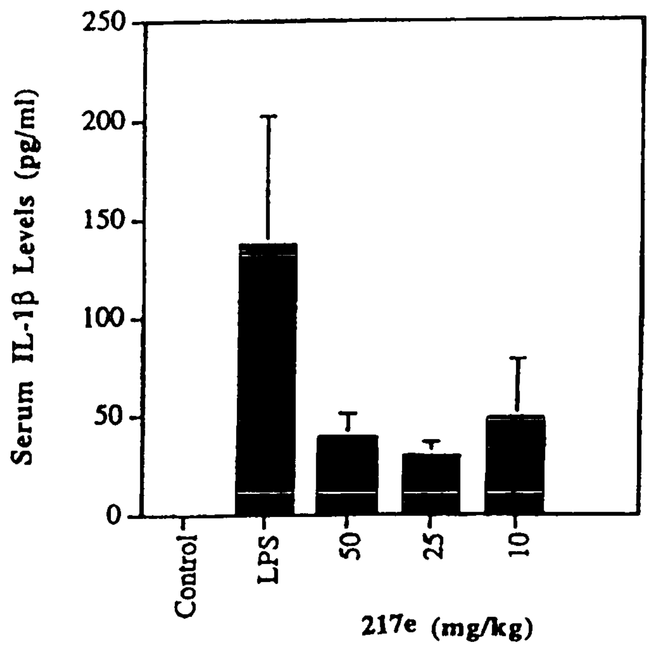
500
400
300
200
100
0
IL-1β pg/mL Serum
214e
404
410
415
417
418
452
456
LPS
Vehicle

FIG. 9



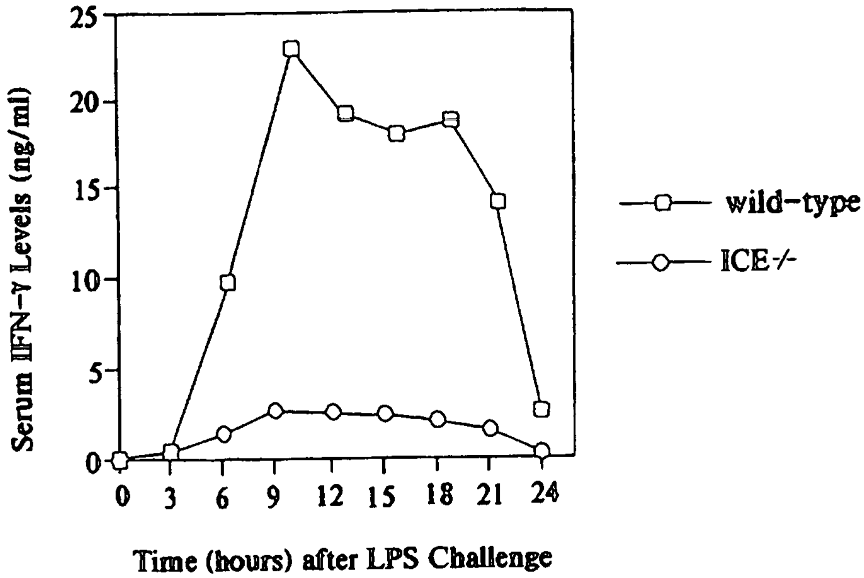
Serum Il-1β Levels (pg/ml)
300
250
200
150
100
50
0
Control
LPS
50
25
10
214e (mg/kg)

FIG. 6



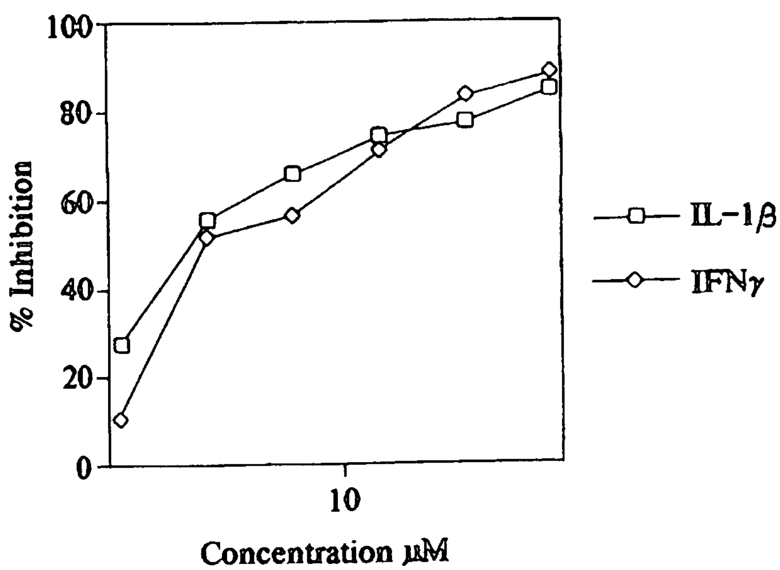
Serum IL-1β Levels (pg/ml)
250
200
150
100
50
0
Control
LPS
50
25
10
217e (mg/kg)

FIG. 7



Serum IFN-γ Levels (ng/ml)
25
20
15
10
5
0
0 3 6 9 12 15 18 21 24
Time (hours) after LPS Challenge
wild-type
ICE-/-

FIG. 4



% Inhibition
100
80
60
40
20
0
10
Concentration µM
IL-1β
IFNγ

FIG. 5

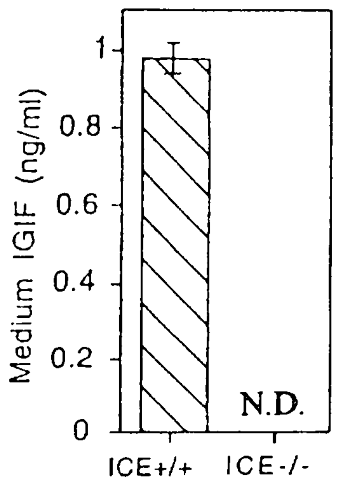


FIG. 3A

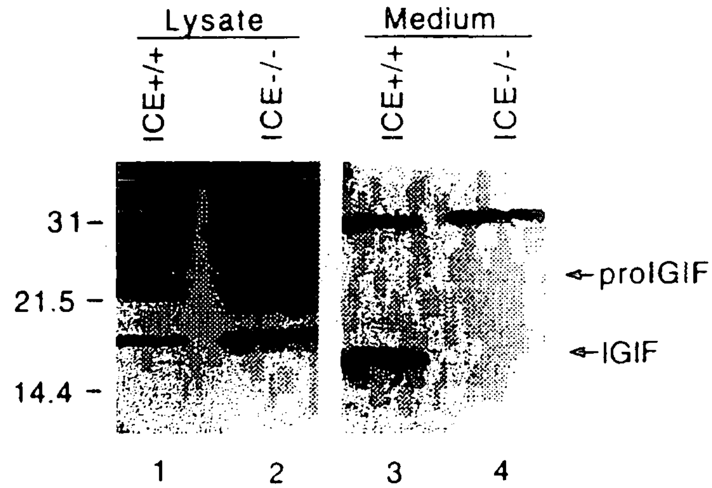


FIG. 3B

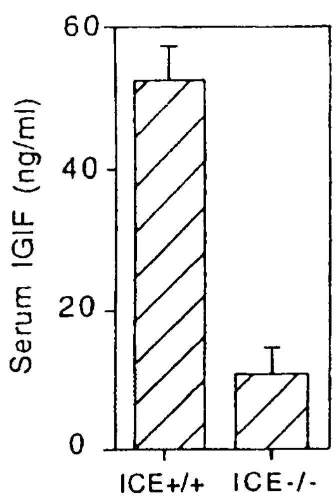


FIG. 3C

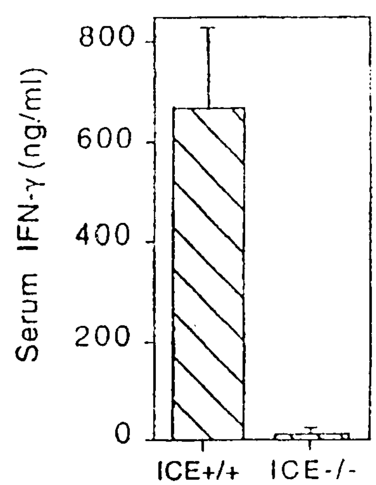
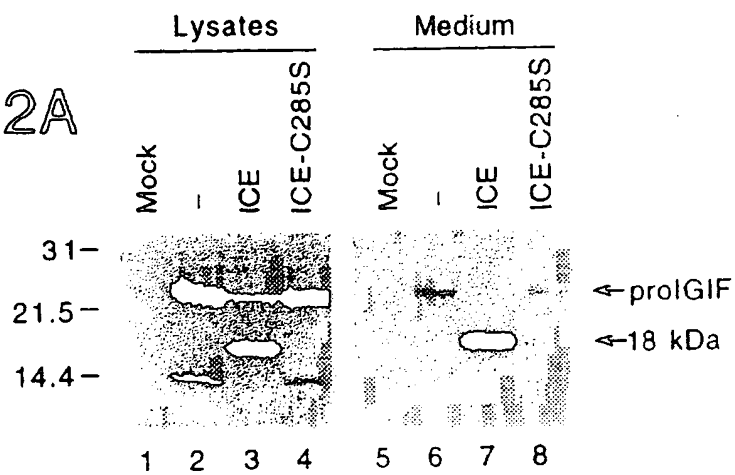


FIG. 3D

FIG. 2A


Lysates
Medium
Mock
-
ICE
ICE-C285S
Mock
-
ICE
ICE-C285S
31—
21.5—
14.4—
←proIGIF
←18 kDa
1 2 3 4 5 6 7 8

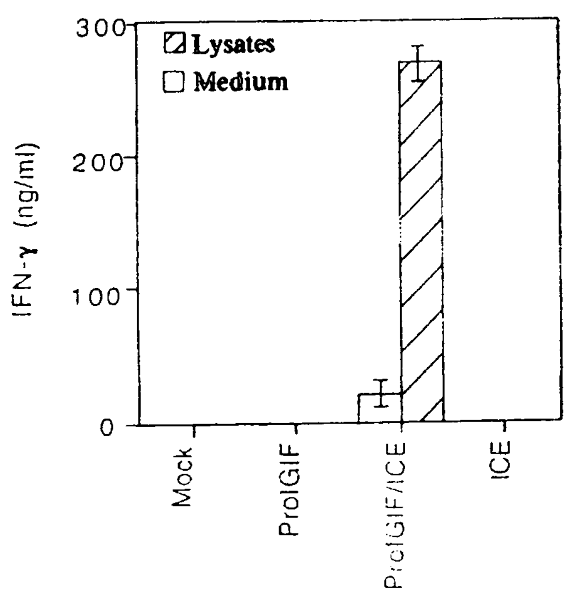

Lysates
Medium
IFN-γ (ng/ml)
300
200
100
0
Mock
ProIGIF
ProIGIF/ICE
ICE

FIG. 2B

FIG. 1A

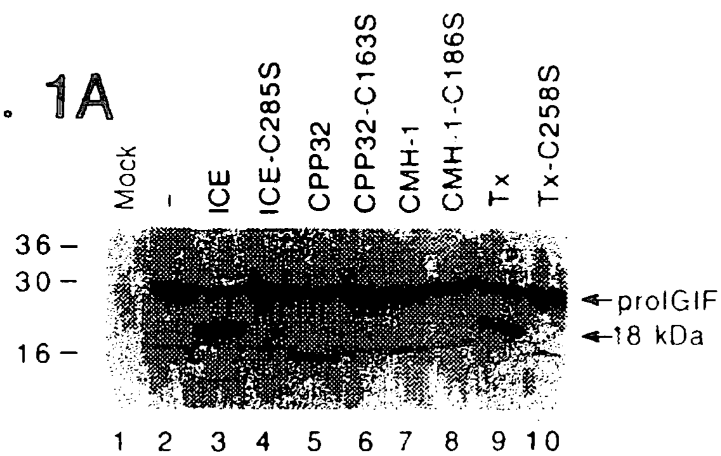


FIG. 1B

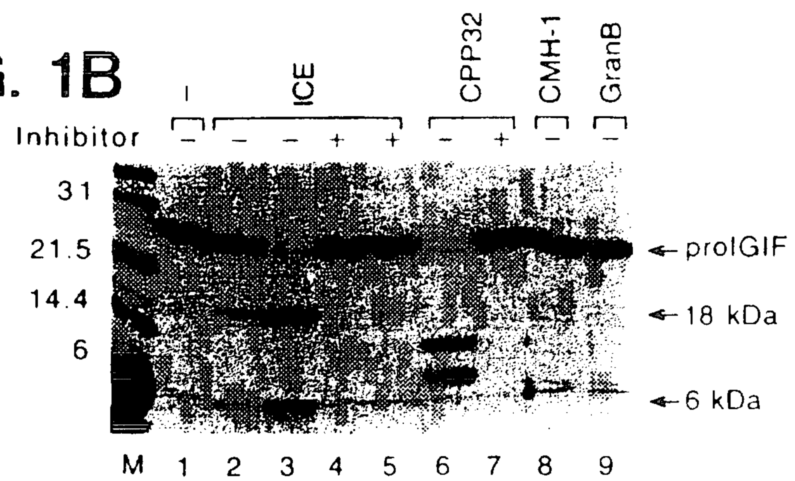
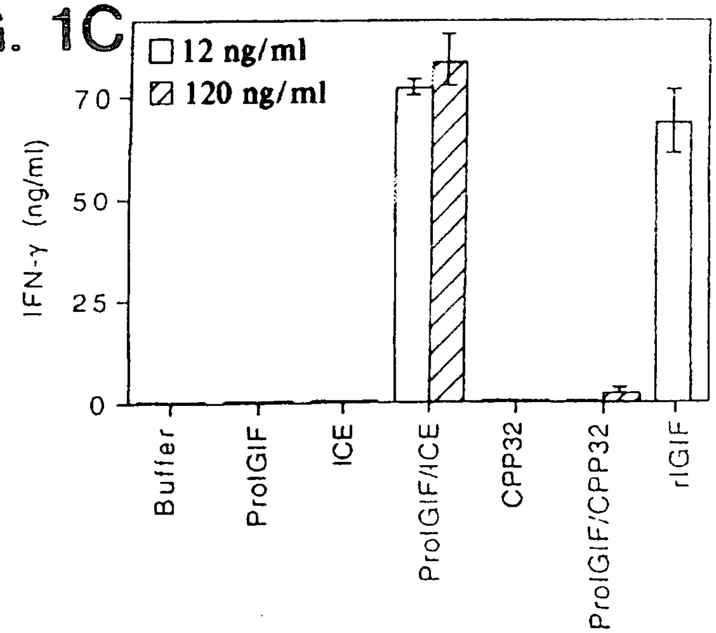
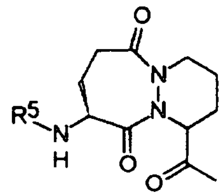
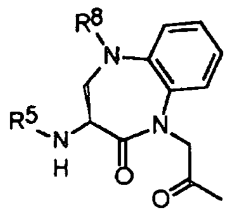


FIG. 1C



(A-e10) 

153. The process according to any one of claims 140-149, wherein R_1 is:

(A-w2) 

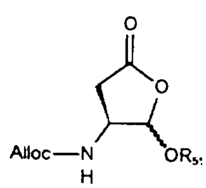
comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

```
 O
/ \
   CH2,
\ /
 O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

151. The process according to any one of claims 140 -149 wherein the N-alloc protected amine is:



, wherein:

R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

152. The process according to any one of claims 140-149, wherein R_1 is:

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

each R_{51} is independently selected from the group consisting of R_9, $-C(O)-R_9$, $-C(O)-N(H)-R_9$, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally

$-C(O)O-R_9$,
$-C(O)-N(R_{10})(R_{10})$
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

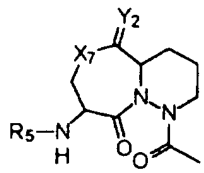
X_5 is CH or N;

Y_2 is H_2 or O;

X_7 is $-N(R_8)-$ or $-O-$;

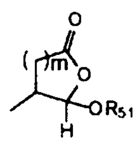
R_6 is selected from the group consisting of -H and $-CH_3$;

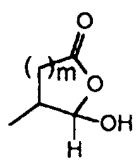
R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
$-H$, and
$-C(O)-C(O)-OR_{10}$;

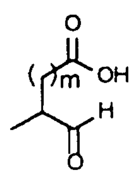
(z)  ; and

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being singly or multiply substituted by halogen, $-NH_2$, or $-NH-R_9$,;

R_2 is:

(a)  ,

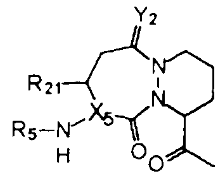
(b)  , or

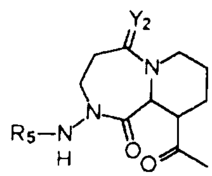
(c)  ;

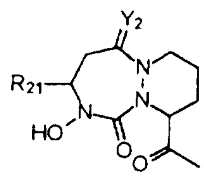
m is 1 or 2;

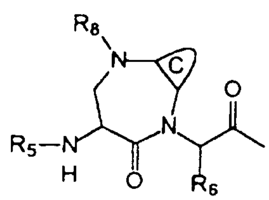
each R_5 is independently selected from the group consisting of:

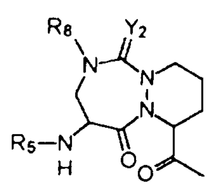
$-C(O)-R_{10}$,

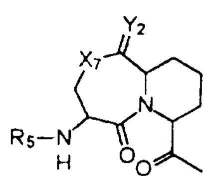
(e10)  ;

(e11)  ;

(e12)  ;

(w2)  ;

(y1)  ;

(y2)  ;

of CH_2Cl_2 and DMF.

145. The process according to claim 144, wherein the nucleophilic scavenger is dimethyl barbituric acid.

146. The process according to claim 145, wherein the solution comprises trifluoroacetic acid in about 1-90% by weight.

147. The process according to claim 146, wherein the solution comprises trifluoroacetic acid in about 20-50% by weight.

148. The process according to claim 145, wherein the solution comprises hydrochloric acid in about 0.1-30% by weight.

149. The process according to claim 148, wherein the solution comprises hydrochloric acid in about 5-15% by weight.

150. The process according to any one of claims 140-149, wherein the N-acylamino compound is represented by formula (VIII):

$$\text{(VIII)} \qquad R_1-\underset{\displaystyle H}{\underset{|}{N}}-R_2$$

wherein:

R_1 is selected from the group consisting of the following formulae:

diabetes mellitus (Type I), juvenile diabetes, psoriasis, graft vs. host disease, and hepatitis.

140. A process for preparing an N-acylamino compound, comprising the steps of:

a) mixing a carboxylic acid with an N-alloc-protected amine in the presence of an inert solvent, triphenylphoshine, a nucleophilic scavenger, and tetrakis-triphenyl phosphine palladium(0) at ambient temperature under an inert atmosphere; and

b) adding to the step a) mixture, HOBT and EDC; and optionally comprising the further step of:

c) hydrolyzing the step b) mixture in the presence of a solution comprising an acid and H_2O, wherein the step b) mixture is optionally concentrated.

141. The process according to claim 140, wherein the inert solvent is CH_2Cl_2, DMF, or a mixture of CH_2Cl_2 and DMF.

142. The process according to claim 140, wherein the nucleophilic scavenger is dimedone, morpholine, trimethylsilyl dimethylamine or dimethyl barbituric acid.

143. The process according to claim 142, wherein the nucleophilic scavenger is trimethylsilyl dimethylamine or dimethyl barbituric acid.

144. The process according to claim 142, wherein the inert solvent is CH_2Cl_2, DMF, or a mixture

production and a pharmaceutically acceptable carrier.

138. A method for treating or preventing a disease selected from an IGIF mediated disease, an IFN-γ mediated disease, an inflammatory disease, an autoimmune disease, an infectious disease, a proliferative disease, a neurodegenerative disease, a necrotic disease, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative collitis, cerebral ischemia, myocardial ischemia, adult respiratory distress syndrome, infectious hepatitis, sepsis, septic shock, Shigellosis, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, acute dermatomyositis, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis and nephrotic syndrome comprising the step of administering to said patient a pharmaceutical composition according to claims 136 or 137.

139. The method according to claim 138, wherein the disease is selected from an inflammatory disease, an autoimmune disease, an infectious disease, rheumatoid arthritis, ulcerative collitis, Crohn's disease, hepatitis, adult respiratory distress syndrome, glomerulonephritis, insulin-dependent

cyclic group is phenyl, substituted by

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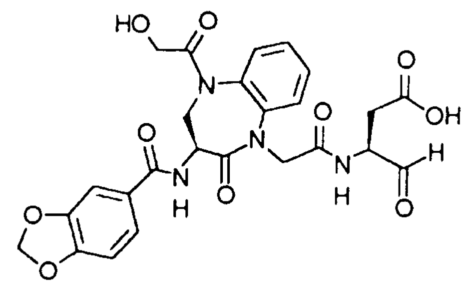
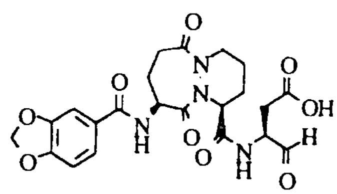
  O
 / \
    CH2
 \ /
  O   .
```

134. The compound according to claim 133, wherein the compound is:

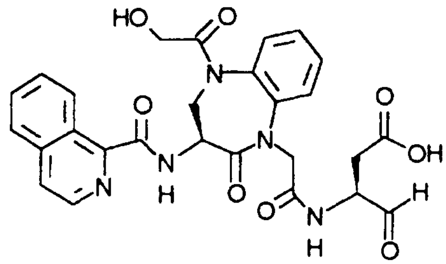
910  .

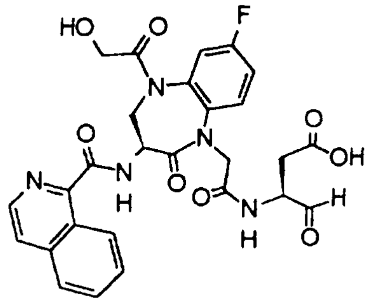
135. The compound according to claim 133, wherein the compound is:

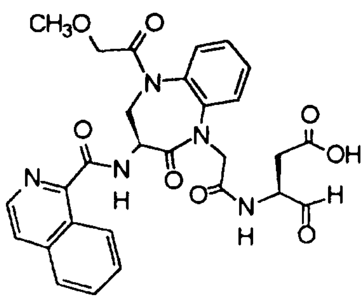
415  .

136. A pharmaceutical composition, comprising a compound according to any one of claims 1-41 and 57-135 in an amount effective for decreasing IGIF production and a pharmaceutically acceptable carrier.

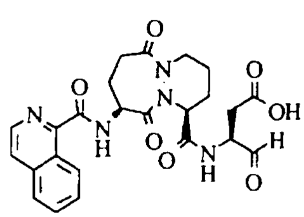
137. A pharmaceutical composition comprising a compound according to any one of claims 1-41 and 57-135 in an amount effective for decreasing IFN-γ

696  ;

696-1  ; and

699  .

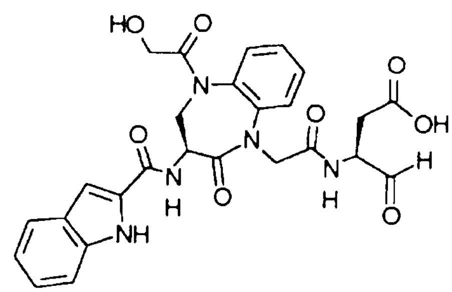
132. The compound according to claim 130, wherein the compound is:

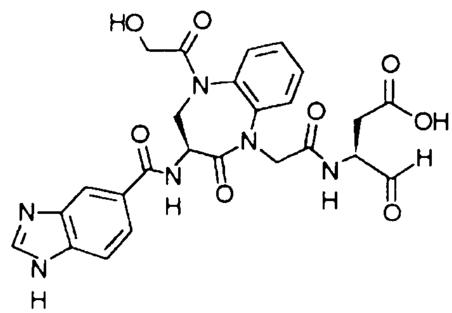
412  .

133. The compound according to claim 119, wherein R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3

by $-Q_1$.

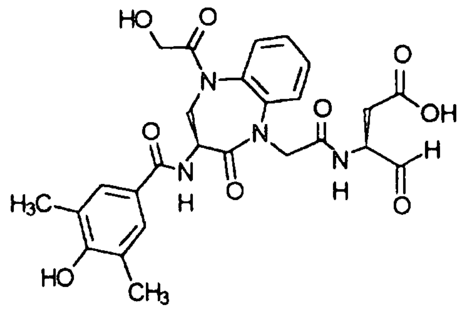
129. The compound according to claim 128, selected from the group consisting of:

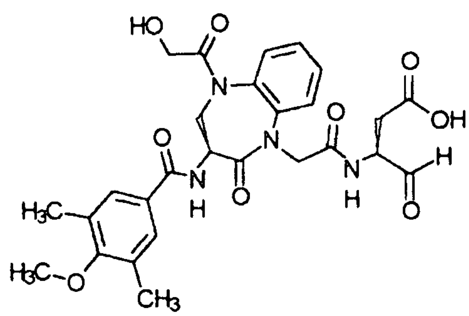
919  ; and

920  .

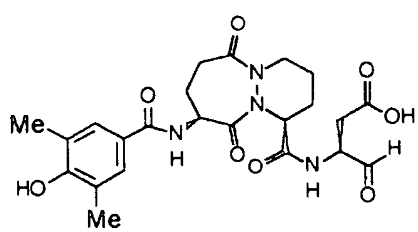
130. The compound according to claim 128, wherein the Ar_3 cyclic group is isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

131. The compound according to claim 130, wherein the compound is:

917  ; and

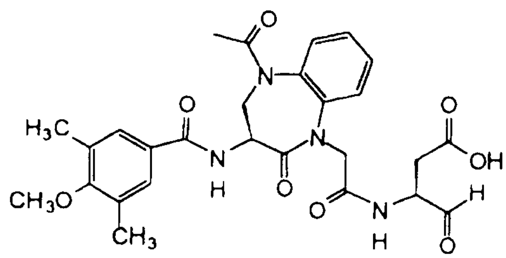
922  .

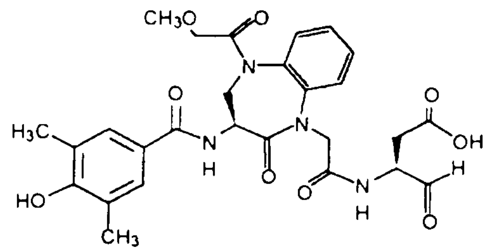
127. The compound according to claim 125, wherein the compound is:

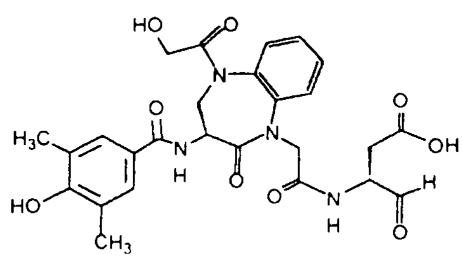
214w  .

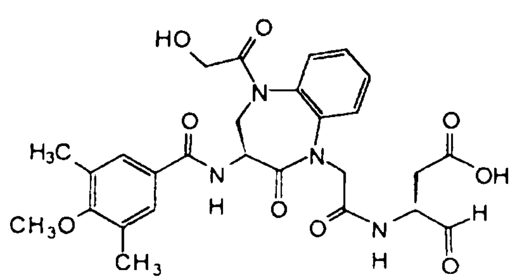
128. The compound according to claim 119, wherein:

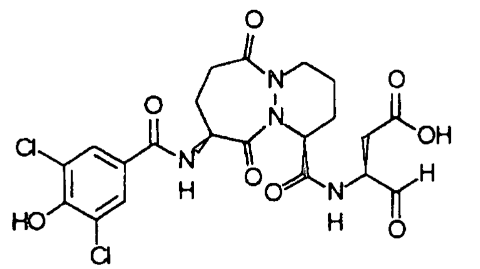
R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted

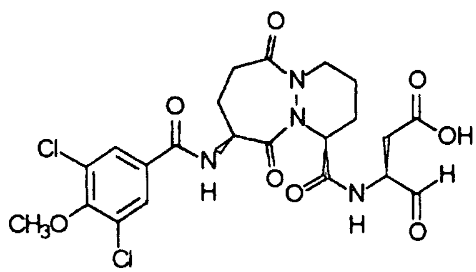
684  ;

689b  ;

691a  ;

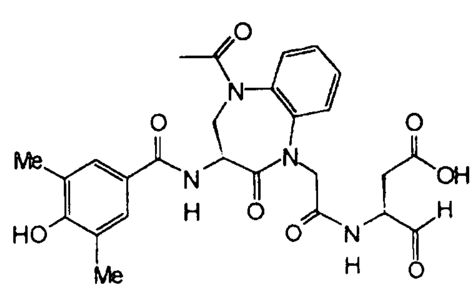
694  ;

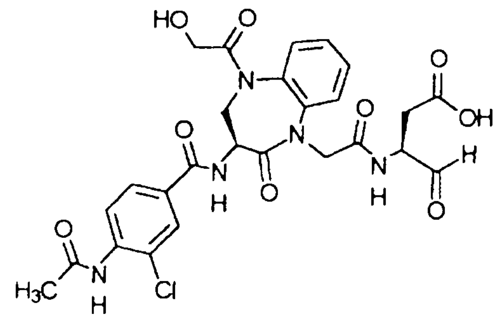
214k  ; and

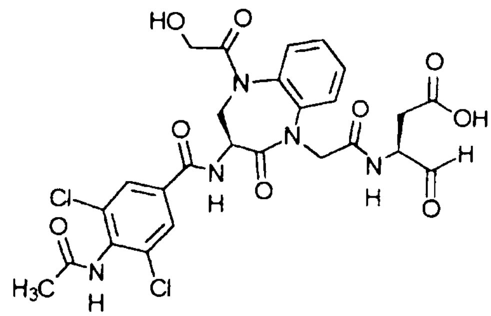
214m  .

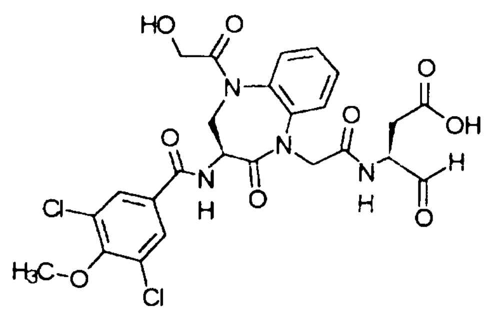
125. The compound according to claim 120, wherein Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by $-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group; and at the 4-position by $-O-R_5$.

126. The compound according to claim 125, selected from the group consisting of:

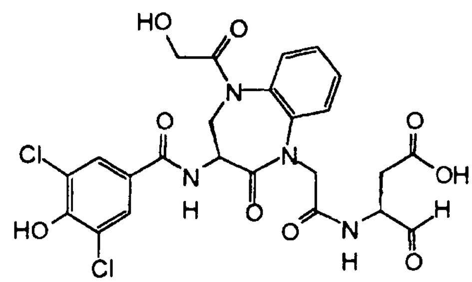
671  ;

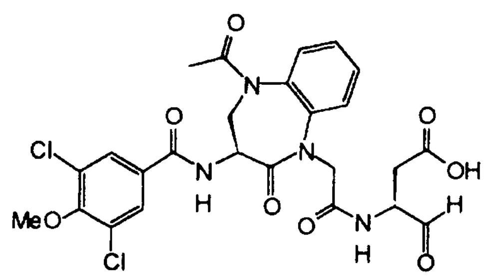
914  ;

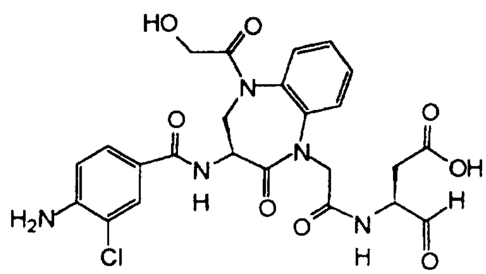
915  ; and

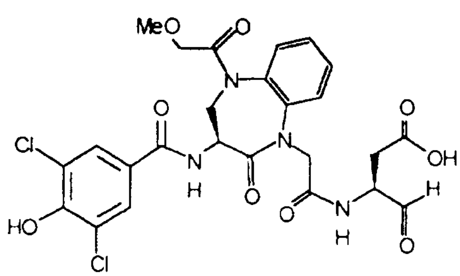
918  .

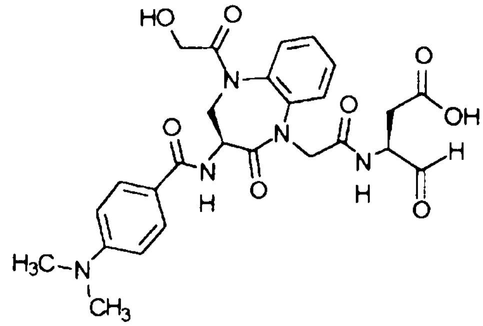
124. The compound according to claim 122, selected from the group consisting of:

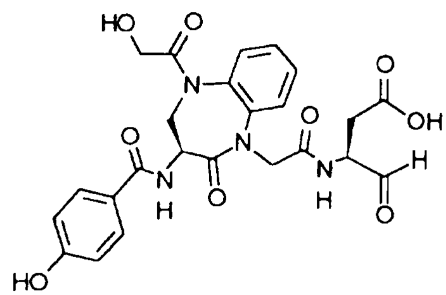
662  ;

669  ;

686  ;

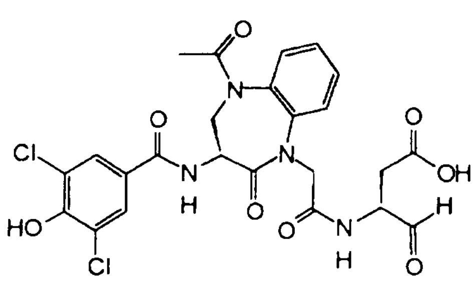
689a  ;

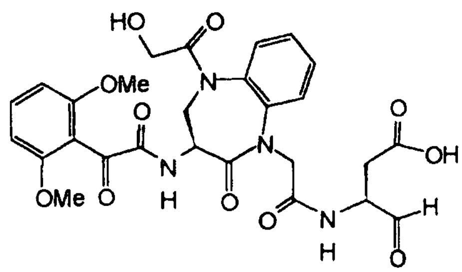
913  ; and

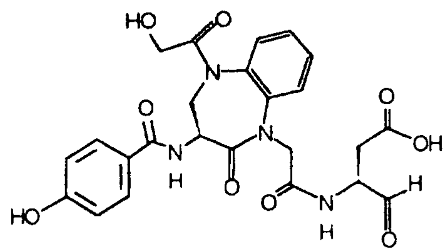
916  .

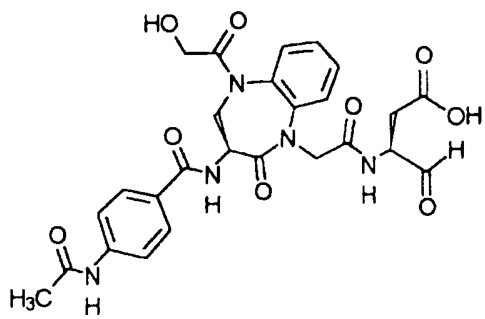
122. The compound according to claim 120, wherein Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by $-NH-R_5$, $-N(R_9)(R_{10})$, or $-O-R_5$.

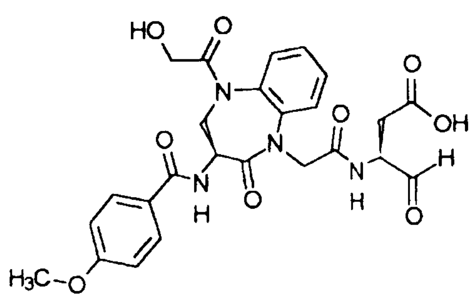
123. The compound according to claim 122, selected from the group consisting of:

656  ;

678  ;

691b  ;

911  ;

912  ;

119. The compound according to claim 118, wherein R_{10} is Ar_3.

120. The compound according to claim 119, wherein:

R_5 is $-C(O)-R_{10}$ and R_{10} is Ar_3, wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

$-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group;

-F,

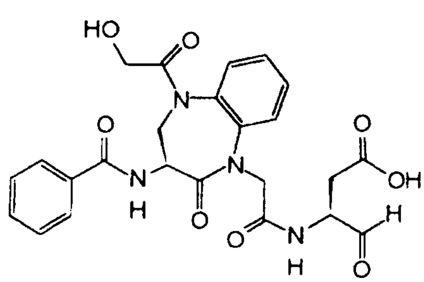
-Cl,

$-N(H)-R_5$, wherein $-R_5$ is -H or $-C(O)-R_{10}$, wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein Ar_3 is phenyl,

$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

121. The compound according to claim 120, selected from the group consisting of:

668  ;

and said cyclic group being singly or multiply substituted by
$-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

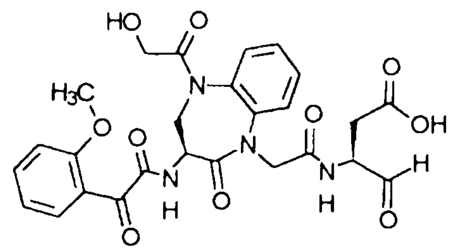
provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

115. The compound according to claim 114, wherein R_3 is $-C(O)-Ar_2$,

116. The compound according to claim 114, wherein R_3 is $-C(O)CH_2-T_1-R_{11}$;

117. The compound according to claim 114, wherein R_3 is -C(O)-H.

118. The compound according to any one of claims 104-117, wherein R_5 is $-C(O)-R_{10}$ or $-C(O)C(O)-R_{10}$.

921 

113. The compound according to claim 111, wherein R_8 is $-C(O)-CH_2-OR_{10}$ and R_{10} is $-H$ or $-CH_3$.

114. The compound according to claim 68, wherein:

m is 1;

T_1 is O or S;

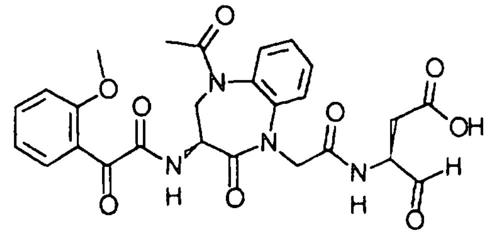
R_{21} is -H or $-CH_3$;

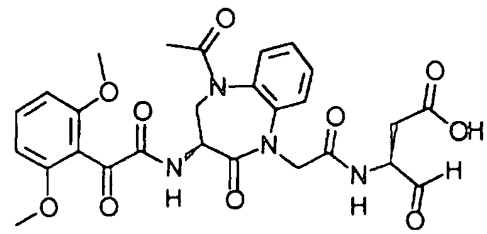
Ar_2 is (hh);

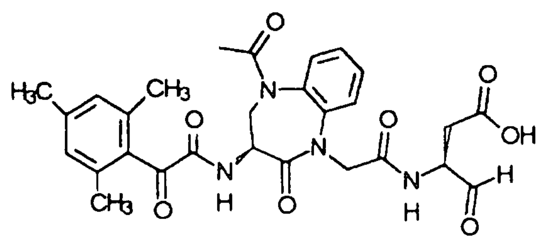
Y is O;

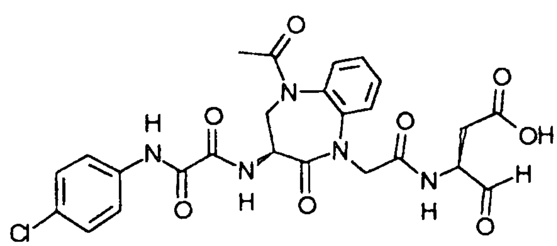
each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl and said cyclic group being singly or multiply substituted by $-Q_1$;

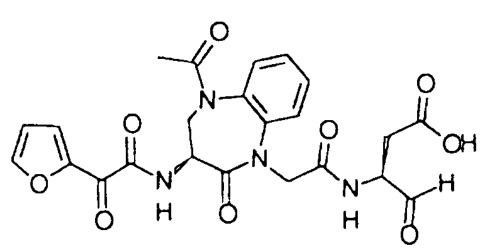
each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl

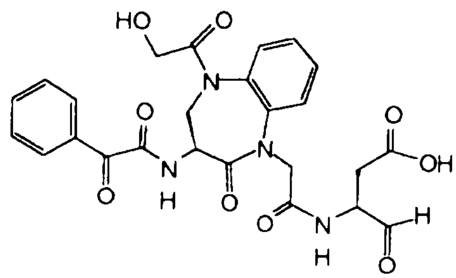
705  ;

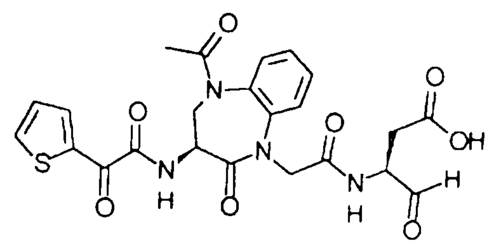
706  ;

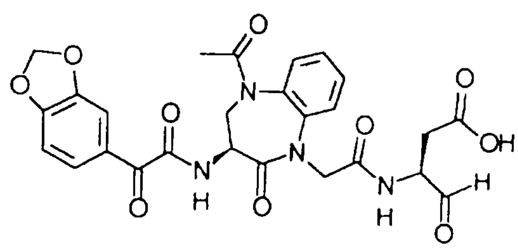
709  ;

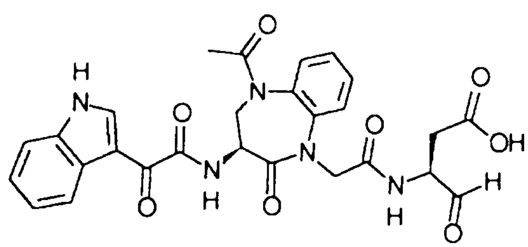
710  ;

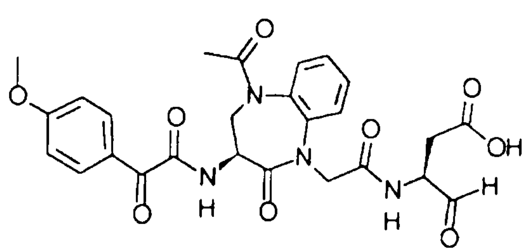
711  ; and

681  ;

701  ;

702  ;

703  ;

704  ;

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-CH_2-OR_{10}$, and
$-C(O)-CH_2C(O)-R_9$.

107. The compound according to claim 106, wherein R_8 is $-C(O)-CH_2-OR_{10}$ and R_{10} is -H or $-CH_3$.

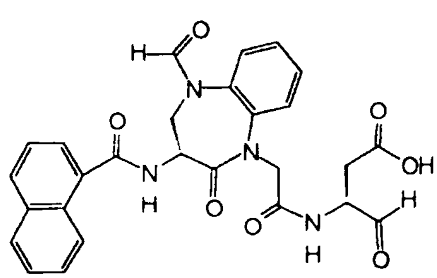
108. The compound according to claim 105, wherein R_3 is $-C(O)-Ar_2$,

109. The compound according to claim 105, wherein R_3 is $-C(O)CH_2-T_1-R_{11}$;

110. The compound according to claim 105, wherein R_3 is -C(O)-H.

111. The compound according to claim 110, wherein R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-CH_2-OR_{10}$, and
$-C(O)-CH_2C(O)-R_9$.

112. The compound according to claim 111, selected from the group consisting of:

653  ;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, thiazolyl, benzimidazolyl, thienothienyl, thiadiazolyl, benzotriazolyl, benzo[b]thiophenyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, naphthyl, pyridinyl, oxazolyl, pyrimidinyl, or indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

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   O
  / \
     CH2,
  \ /
   O
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wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

106. The compound according to claim 105, wherein R_8 is selected from the group consisting of:

=O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

```
 O
/ \
   CH2;
\ /
 O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

105. The compound according to claim 104, wherein:

m is 1;

C is a ring chosen from the set consisting of benzo, pyrido, and thieno, the ring optionally being singly or multiply substituted by halogen, $-NH_2$, $-NH-R_5$, or $-NH-R_9$, $-OR_{10}$, or $-R_9$, wherein R_9 is a straight or branched C_{1-4} alkyl group, and R_{10} is H or a straight or branched C_{1-4} alkyl group;

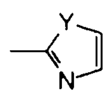
T_1 is O or S;

R_6 is H;

R_{11} is selected from the group consisting of $-Ar_4$, $-(CH_2)_{1-3}-Ar_4$, and $-C(O)-Ar_4$;

Ar_2 is (hh);

Y is O;

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN,

alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

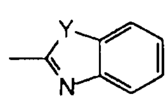
each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh) 

, and

$-C(O)O-R_9$,
$-C(O)-N(R_{10})(R_{10})$
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

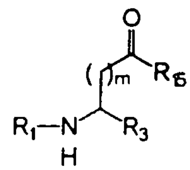
each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
$-H$, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched

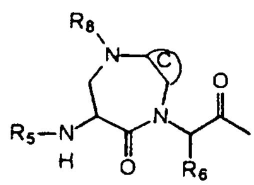
104. A compound represented by the formula:

(VII) 

wherein:

m is 1 or 2;

R_1 is selected from the group consisting of the following formulae:

(w2)  ;

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl, the ring optionally being singly or multiply substituted by $-Q_1$,;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

$-C(O)-CH_2-T_1-R_{11}$,

$-C(O)-CH_2-F$,

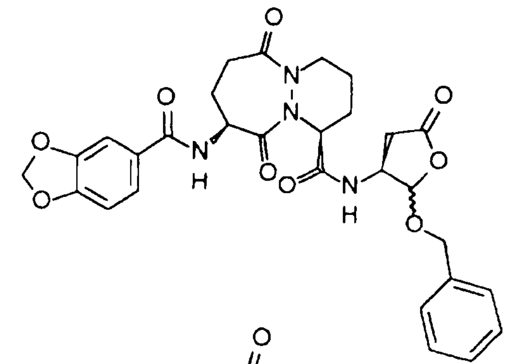
$-C=N-O-R_9$, and

$-CO-Ar_2$;

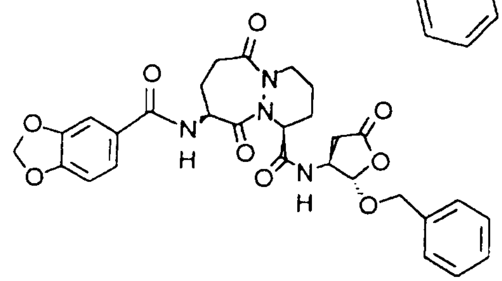
each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

213n

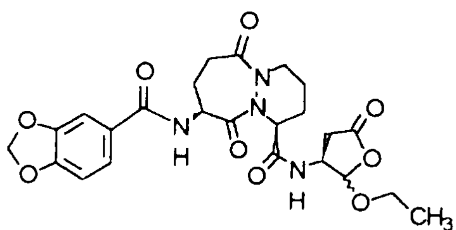


415a



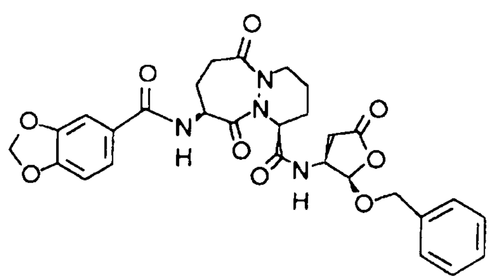
;

415b

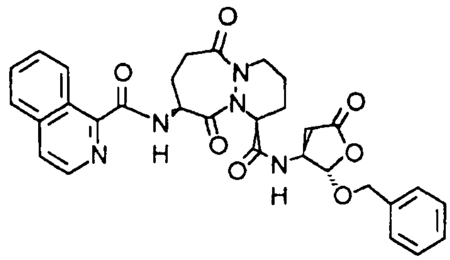


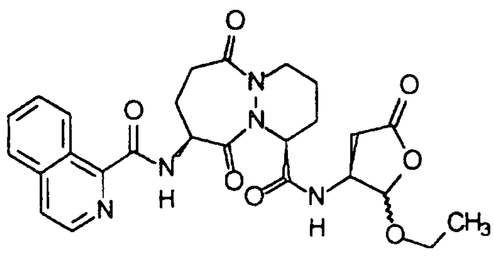
; and

415c



.

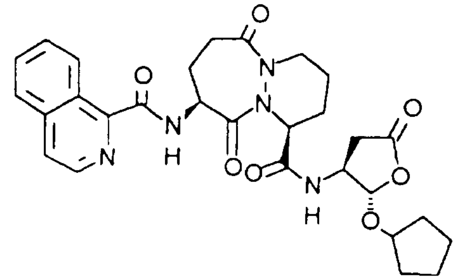
412h  ; and

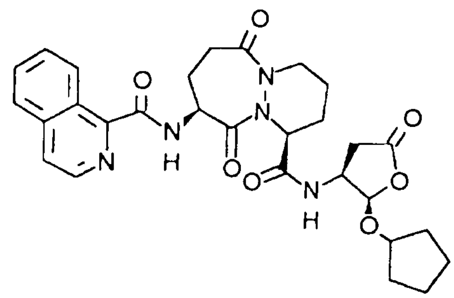
550q  .

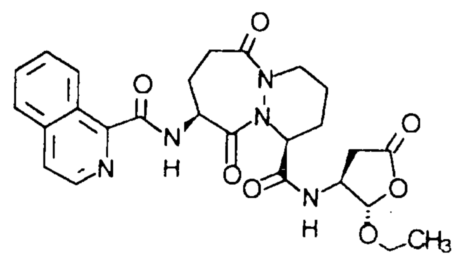
102. The compound according to claim 89, wherein R_5 is -C(O)-R_{10}, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is phenyl, substituted by

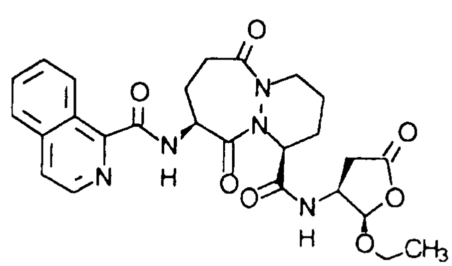
```
  O
 / \
    CH2
 \ /
  O   .
```

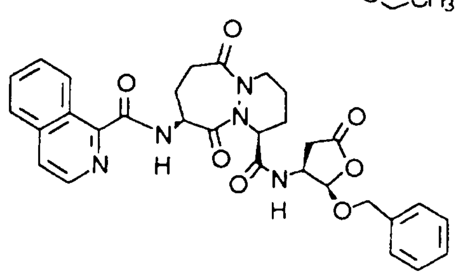
103. The compound according to claim 102, selected from the group consisting of:

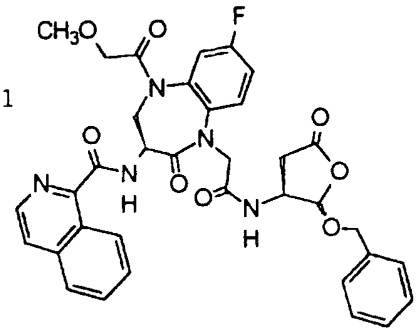
412c  ;

412d  ;

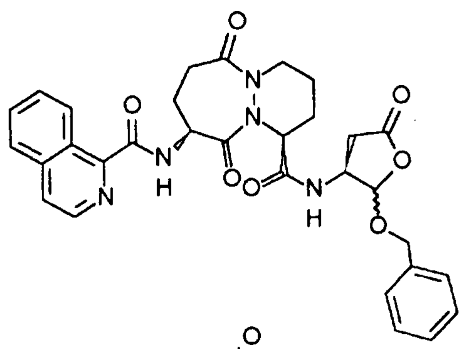
412e  ;

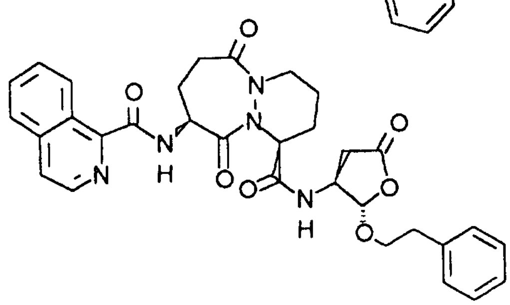
412f  ;

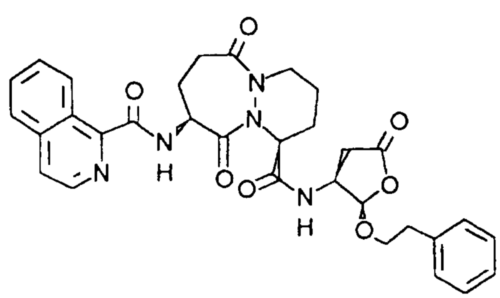
412g  ;

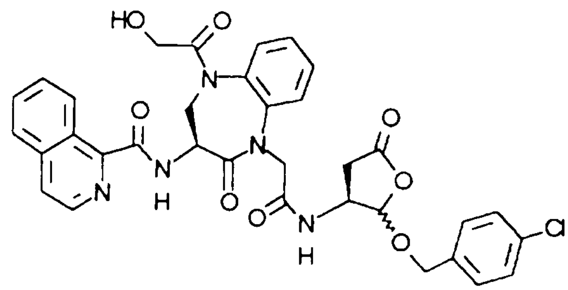
699a-1  .

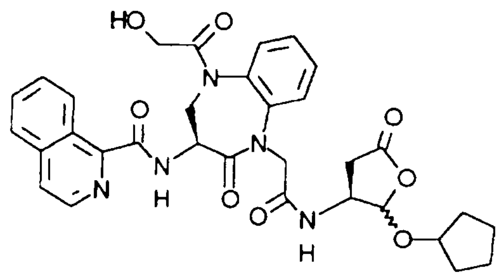
101. The compound according to claim 99, selected from the group consisting of:

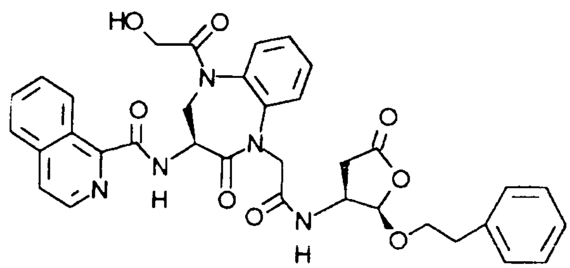
213y  ;

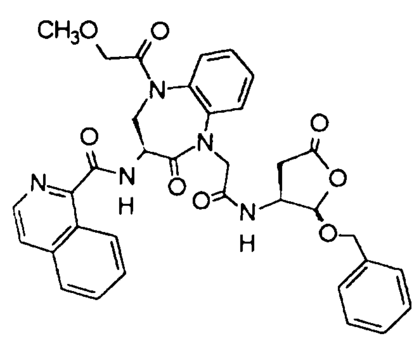
412a  ;

412b  ;

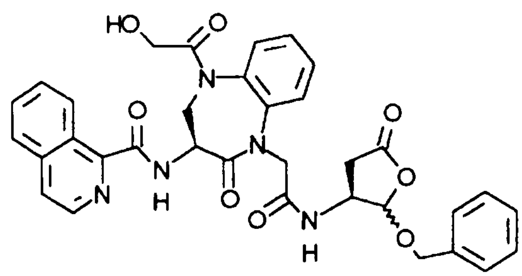
696c  ;

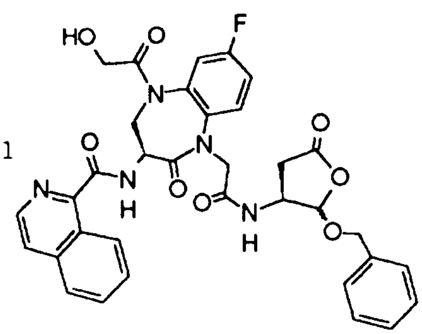
696d  ;

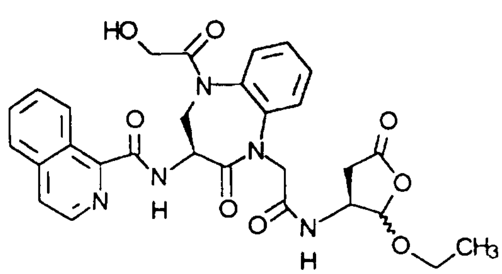
696e  ;

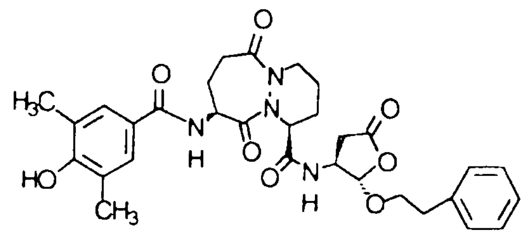
699a  ; and

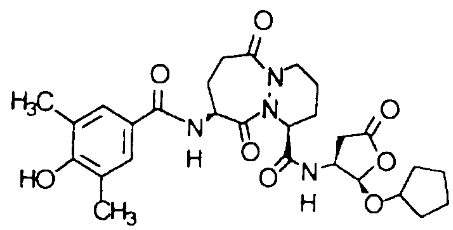
100. The compound according to claim 99 selected from the group consisting of:

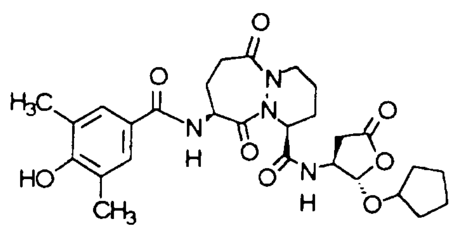
696a  ;

696a-1  ;

696b  ;

214w-5  ;

214w-6  ; and

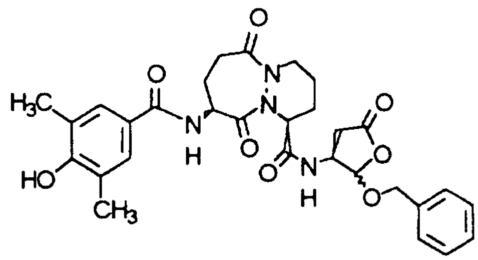
214w-7  .

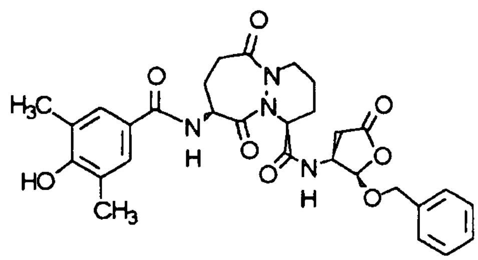
98. The compound according to claim 89, wherein:

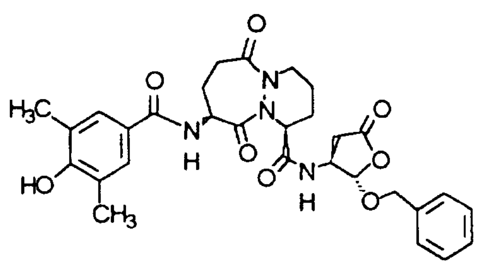
R_5 is -C(O)-R_{10}, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, quinolyl, isoquinolyl and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by -Q_1.

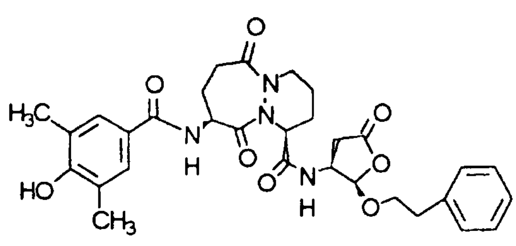
99. The compound according to claim 98, wherein the Ar_3 cyclic group is isoquinolyl, and said cyclic group optionally being singly or multiply substituted by -Q_1.

97. The compound according to claim 95, selected from the group consisting of:

214w-1  ;

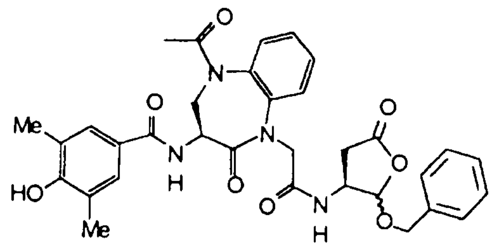
214w-2  ;

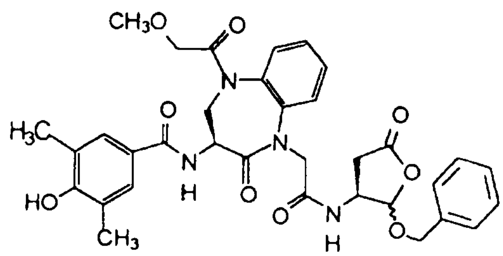
214w-3  ;

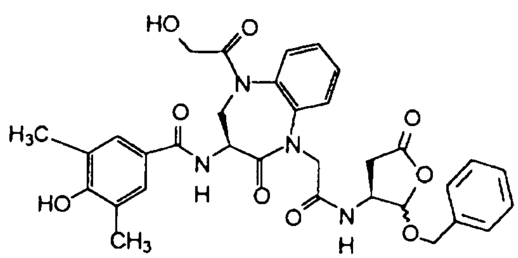
214w-4  ;

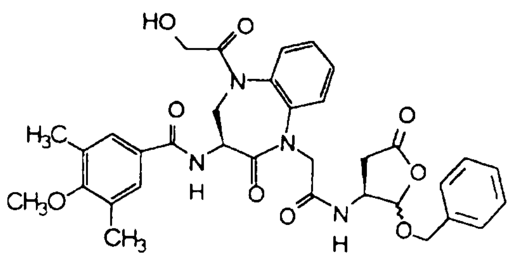
and at the 4-position by $-O-R_5$.

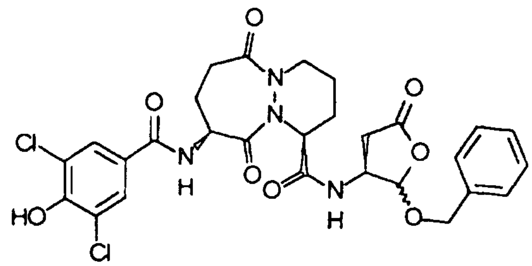
96. The compound according to claim 95, selected from the group consisting of:

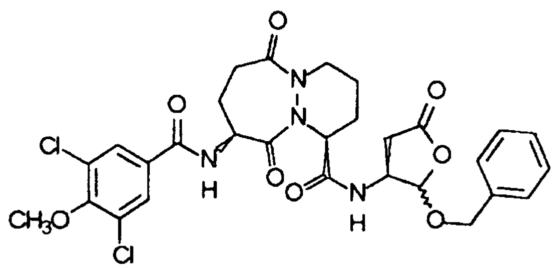
670  ;

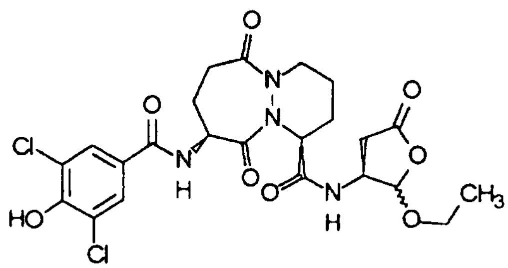
688b  ;

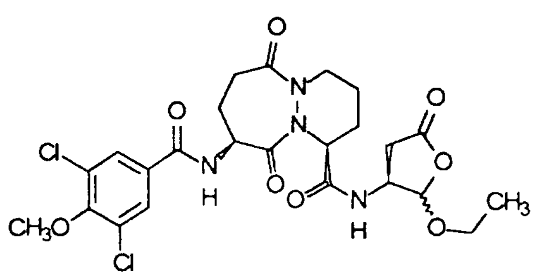
690a  ; and

695c  .

213k  ;

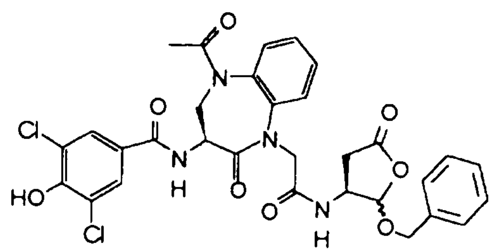
213m  ;

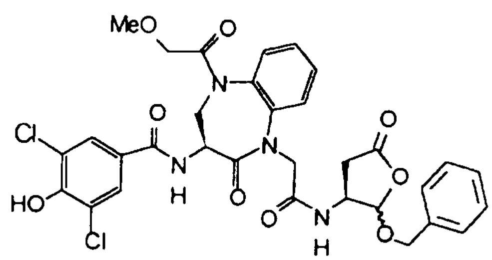
550k  ; and

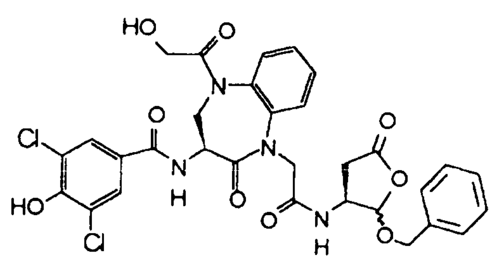
550m  .

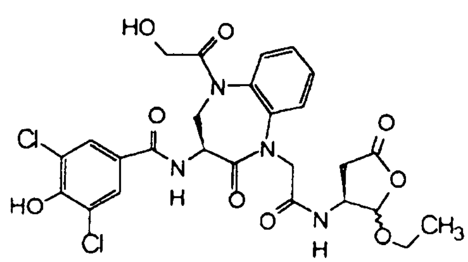
95. The compound according to claim 90, wherein Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by $-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group;

93. The compound according to claim 92, selected from the group consisting of:

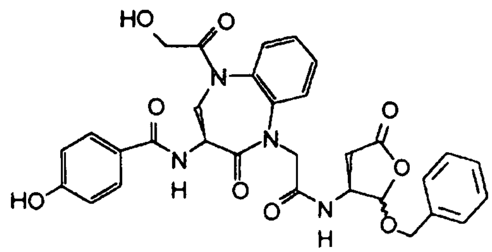
655  ;

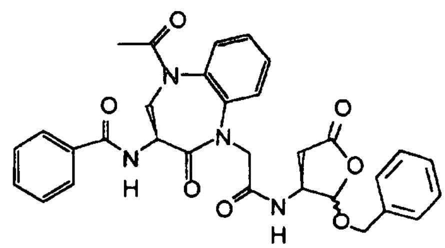
688a  ;

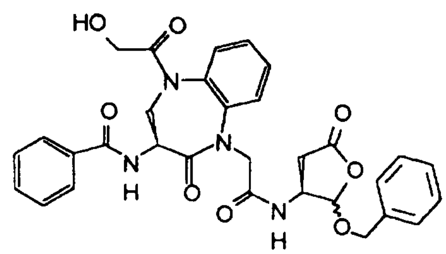
692a  ; and

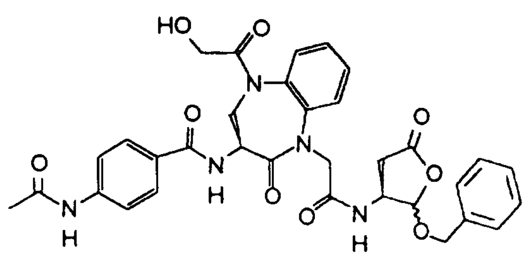
692b  .

94. The compound according to claim 92, selected from the group consisting of:

690b  ;

693  ;

695a  ; and

695b  .

92. The compound according to claim 90, wherein Ar_3 is phenyl being singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by $-NH-R_5$, $-N(R_9)(R_{10})$, or $-O-R_5$.

89. The compound according to claim 88, wherein R_{10} is Ar_3.

90. The compound according to claim 89, wherein:

R_5 is $-C(O)-R_{10}$ and R_{10} is Ar_3, wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

$-R_9$, wherein R_9 is a C_{1-4} straight or branched alkyl group;

-F,

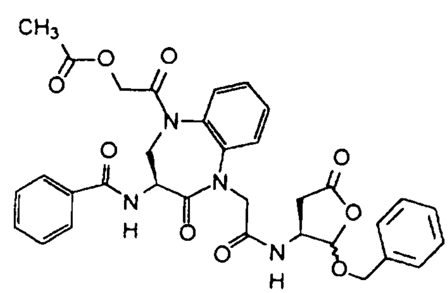
-Cl,

$-N(H)-R_5$, wherein $-R_5$ is -H or $-C(O)-R_{10}$, wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein Ar_3 is phenyl,

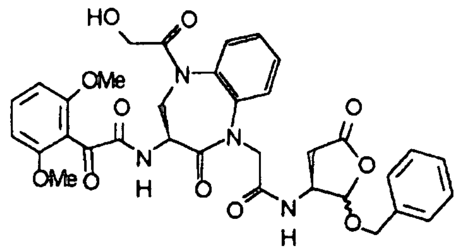
$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

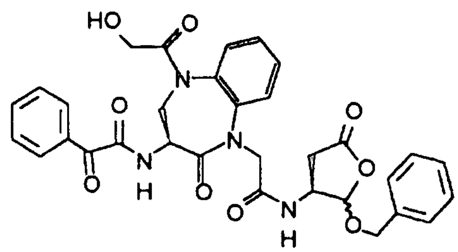
$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

91. The compound according to claim 90, selected from the group consisting of:

682  ;

selected from the group consisting of:

677  ; and

680  .

84. The compound according to claim 82, wherein R_8 is selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

$-C(O)-CH_2-OR_{10}$, and

$-C(O)-CH_2C(O)-R_9$.

85. The compound according to claim 84, wherein R_8 is $-C(O)-CH_2-OR_{10}$ and R_{10} is -H or $-CH_3$.

86. The compound according to claim 81, wherein R_1 is (e10) and X_5 is CH.

87. The compound according to claim 81, wherein R_1 is (e10) and X_5 is N.

88. The compound according to any one of claims 80-87 wherein R_5 is $-C(O)-R_{10}$ or $-C(O)-C(O)-R_{10}$.

optionally substituted with $-Ar_3$, wherein Ar_3 is phenyl, optionally substituted by $-Q_1$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

82. The compound according to claim 81, wherein R_1 is (w2).

83. The compound according to claim 82,

consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

```
 O
/ \
   CH2,
\ /
 O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

81. The compound according to claim 80, wherein:

m is 1;

C is a ring chosen from the set consisting of benzo, pyrido, or thieno the ring optionally being singly or multiply substituted by halogen, $-NH_2$, $-NH-R_5$, $-NH-R_9$, $-OR_{10}$, or $-R_9$, wherein R_9 is a straight or branched C_{1-4} alkyl group, and R_{10} is H or a straight or branched C_{1-4} alkyl group;

R_6 is H;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted by $-Q_1$;

R_{21} is -H or $-CH_3$;

R_{51} is a C_{1-6} straight or branched alkyl group

each R_{10} is independently selected from the group consisting of -H, -Ar_3, a -C_{3-6} cycloalkyl group, and a -C_{1-6} straight or branched alkyl group optionally substituted with -Ar_3, wherein the -C_{1-6} alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a -C_{1-6} straight or branched alkyl group optionally substituted with -Ar_3, -$CONH_2$, -OR_5, -OH, -OR_9, or -CO_2H;

each R_{51} is independently selected from the group consisting of R_9, -C(O)-R_9, -C(O)-N(H)-R_9, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

each R_{21} is independently selected from the group consisting of -H or a -C_{1-6} straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Q_1 is independently selected from the group

$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

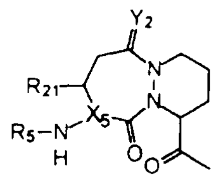
X_5 is CH or N;

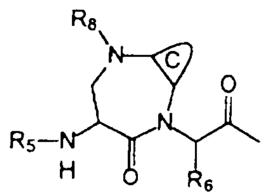
Y_2 is H_2 or O;

R_6 is selected from the group consisting of -H and $-CH_3$;

R_8 is selected from the group consisting of:
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(H)-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$;
$-C(O)-CH_2N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

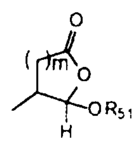
each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

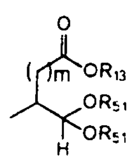
(e10)  , or

(w2)  ;

C is a ring chosen from the set consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl; the ring optionally being singly or multiply substituted by $-Q_1$;

R_2 is:

(a)  , or

(b)  ;

m is 1 or 2;

each R_5 is independently selected from the group consisting of:

$-C(O)-R_{10}$,

$-C(O)O-R_9$,

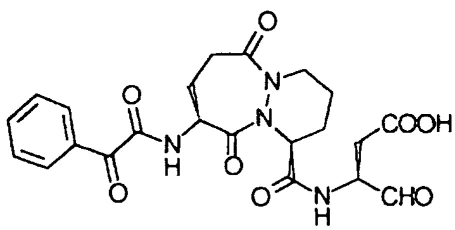
$-C(O)-N(R_{10})(R_{10})$

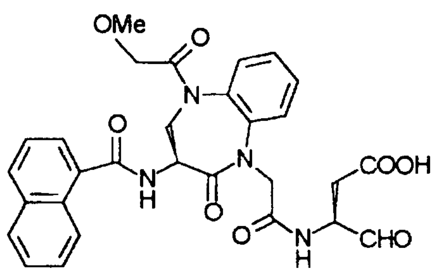
R_3 is -C(O)-H; and

R_5 is -C(O)-R_{10}, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is phenyl, substituted by

```
  O
 / \
    CH2
 \ /
  O   .
```

79. The compound according to claim 68, selected from the group consisting of:

2002  ; and

2201  .

80. A compound represented by the formula:

```
(VI)      R1-N-R2
             |
             H
```

wherein:

R_1 is:

phenyl,

$-N(R_9)(R_{10})$, wherein R_9 and R_{10} are independently a $-C_{1-4}$ straight or branched alkyl group, or

$-O-R_5$, wherein R_5 is H or a $-C_{1-4}$ straight or branched alkyl group.

75. The compound according to claim 74, wherein Ar_3 is phenyl being optionally singly or multiply substituted at the 3- or 5-position by -Cl or at the 4-position by $-NH-R_5$, $-N(R_9)(R_{10})$, or $-O-R_5$.

76. The compound according to claim 68, wherein:

R_3 is -C(O)-H;

R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from the group consisting of is indolyl, benzimidazolyl, thienyl, and benzo[b]thiophenyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

77. The compound according to claim 68, wherein:

R_3 is -C(O)-H; and

R_5 is $-C(O)-R_{10}$, wherein R_{10} is Ar_3 and the Ar_3 cyclic group is selected from quinolyl and isoquinolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$.

78. The compound according to claim 66, wherein:

is $-C(O)-Ar_4$, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$ and the Ar_3 cyclic group is phenyl.

69. The compound according to claim 68, wherein R_{21} is $-CH_3$.

70. The compound according to claim 68, wherein R_5 is $-C(O)-C(O)-OR_{10}$.

71. The compound according to claim 68, wherein R_5 is $-C(O)-C(O)-OR_{10}$ and R_{21} is $-CH_3$.

72. The compound according to any one of claims 66, 67, 70 and 71, wherein R_3 is $-C(O)-H$.

73. The compound according to any one of claims 65, 68 and 69, wherein R_3 is $-C(O)-H$.

74. The compound according to claim 68, wherein:

R_3 is $-C(O)-H$, and

R_5 is $-C(O)-R_{10}$, wherein:

R_{10} is Ar_3, wherein the Ar_3 cyclic group is phenyl optionally being singly or multiply substituted by:

$-F$,

$-Cl$,

$-N(H)-R_5$, wherein $-R_5$ is $-H$ or $-C(O)-R_{10}$, wherein R_{10} is a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein Ar_3 is

4-(carboxyethyl)phenyl, 4-(carboxypropyl)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

-C(O)-OR_9, wherein R_9 is isobutyl or -CH_2-Ar_3 and the Ar_3 cyclic group is phenyl;

and when R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-phenyl-3-trifluoromethyl)pyrazolyl or 5-(1-(4-chloro-2-pyridinyl)-3-trifluoromethyl)pyrazolyl, then R_5 cannot be:

-C(O)-OR_9, wherein R_9 is -CH_2-Ar_3, and the Ar_3 cyclic group is phenyl;

and when R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-(2-pyridyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

-C(O)-R_{10}, wherein R_{10} is -Ar_3 and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, or

-C(O)-OR_9, wherein R_9 is -CH_2-Ar_3, and the Ar_3 cyclic group is phenyl, unsubstituted by -Q_1; and when

Y_2 is O, R_3 is -C(O)-CH_2-T_1-R_{11}, T_1 is O, and R_{11} is -C(O)-Ar_4, wherein the Ar_4 cyclic group is 2,5-dichlorophenyl, then R_5 cannot be:

-C(O)-R_{10}, wherein R_{10} is -Ar_3 and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, 4-(N-morpholinomethyl)phenyl, 4-(N-methylpiperazino)methyl)phenyl, 4-(N-(2-methyl)imidazolylmethyl)phenyl, 5-benzimidazolyl, 5-benztriazolyl, N-carboethoxy-5-benztriazolyl, N-carboethoxy-5-benzimidazolyl, or

-C(O)-OR_9, wherein R_9 is -CH_2-Ar_3, and the Ar_3 cyclic group is phenyl, unsubstituted by -Q_1,; and when

Y_2 is H_2, R_3 is -C(O)-CH_2-T_1-R_{11}, T_1 is O, and R_{11}

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

```
  O
 / \
    CH2;
 \ /
  O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$;

provided that when:

m is 1;
R_{15} is -OH;
R_{21} is -H; and

Y_2 is O and R_3 is -C(O)-H, then R_5 cannot be:

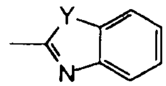
$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$, 4-(carboxymethoxy)phenyl, 2-fluorophenyl, 2-pyridyl, N-(4-methylpiperazino)methylphenyl, or

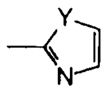
$-C(O)-OR_9$, wherein R_9 is $-CH_2-Ar_3$, and the Ar_3 cyclic group is phenyl, unsubstituted by $-Q_1$; and when

Y_2 is O, R_3 is $-C(O)-CH_2-T_1-R_{11}$, T_1 is O, and R_{11} is Ar_4, wherein the Ar_4 cyclic group is 5-(1-(4-chlorophenyl)-3-trifluoromethyl)pyrazolyl), then R_5 cannot be:

-H;

$-C(O)-R_{10}$, wherein R_{10} is $-Ar_3$ and the Ar_3 cyclic group is 4-(dimethylaminomethyl)phenyl, phenyl, 4-(carboxymethylthio)phenyl,4-(carboxyethylthio)phenyl,

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -N(R_5)-, and -N(R_9)- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -Q_1;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)$_2$-;

each R_9 is independently selected from the group consisting of -Ar_3 and a -C_{1-6} straight or branched alkyl group optionally substituted with -Ar_3, wherein the -C_{1-6} alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, -Ar_3, a -C_{3-6} cycloalkyl group, and a -C_{1-6} straight or branched alkyl group optionally substituted with -Ar_3, wherein the -C_{1-6} alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

-Ar_4,
-$(CH_2)_{1-3}$-Ar_4,
-H, and
-C(O)-Ar_4;

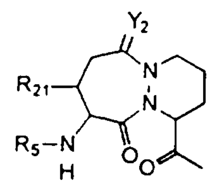
R_{15} is selected from the group consisting of -OH, -OAr_3, -N(H)-OH, and -OC_{1-6}, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with -Ar_3, -$CONH_2$, -OR_5, -OH, -OR_9, or -CO_2H;

each R_{21} is independently selected from the group consisting of -H or a -C_{1-6} straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q_1 or phenyl, optionally substituted by Q_1:

m is 1 or 2;

R_1 is:

(e10-B)  ;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

-C(O)-CH_2-T_1-R_{11},

-C(O)-CH_2-F,

-C=N-O-R_9, and

-CO-Ar_2;

each R_5 is independently selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

-C(O)-N(R_{10})(R_{10})

-S(O)$_2$-R_9,

-S(O)$_2$-NH-R_{10},

-C(O)-CH_2-O-R_9,

-C(O)C(O)-R_{10},

-R_9,

-H,

-C(O)C(O)-OR_{10}, and

-C(O)C(O)-N(R_9)(R_{10});

Y_2 is H_2 or O;

from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

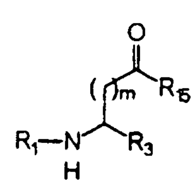
each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

```
 O
/ \
   CH2;
\ /
 O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

67. The compound according to claim 66, wherein R_{21} is $-CH_3$.

68. A compound represented by the formula:

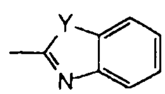
(V) 

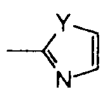
wherein:

$-Ar_3$, $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected

$-C(O)-H$,
$-C(O)-CH_2-T_1-R_{11}$,
$-C(O)-CH_2-F$,
$-C=N-O-R_9$, and
$-CO-Ar_2$;

each R_5 is $-C(O)C(O)-OR_{10}$;

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with

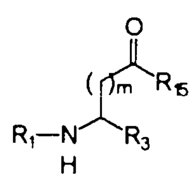
containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

```
  O
 / \
    CH2;
 \ /
  O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

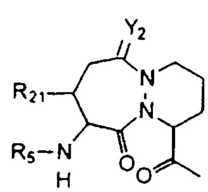
66. A compound represented by the formula:

(V) 

wherein:

m is 1 or 2;

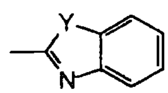
R_1 is:

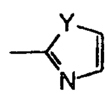
(e10-B)  ;

R_3 is selected from the group consisting of:

-CN,

group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally

$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

Y_2 is H_2 or O;

each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and $-S(O)_2-$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

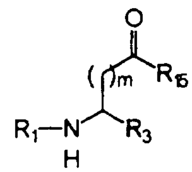
each R_{11} is independently selected from the group consisting of:

$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with $-Ar_3$, $-CONH_2$, $-OR_5$, -OH, $-OR_9$, or $-CO_2H$;

R_{21} is $-CH_3$;

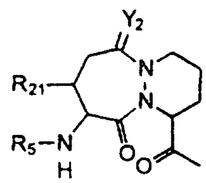
Ar_2 is independently selected from the following

(V) 

wherein:

m is 1 or 2;

R_1 is:

(e10-B)  ;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

-C(O)-CH_2-T_1-R_{11},

-C(O)-CH_2-F,

-C=N-O-R_9, and

-CO-Ar_2;

each R_5 is independently selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

-C(O)-N(R_{10})(R_{10})

-S(O)$_2$-R_9,

-S(O)$_2$-NH-R_{10},

-C(O)-CH_2-O-R_9,

-C(O)C(O)-R_{10},

-R_9,

-H,

from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, -NH-, -$N(R_5)$-, and -$N(R_9)$- said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or muitiply substituted by -Q_1;

each Q_1 is independently selected from the group consisting of -NH_2, -CO_2H, -Cl, -F, -Br, -I, -NO_2, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, -OR_5, -NHR_5, -OR_9, -$N(R_9)(R_{10})$, -R_9, -$C(O)$-R_{10}, and

```
 O
/ \
   CH2;
\ /
 O
```

provided that when -Ar_3 is substituted with a Q_1 group which comprises one or more additional -Ar_3 groups, said additional -Ar_3 groups are not substituted with another -Ar_3.

63. The compound according to claim 62, wherein R_1 is (w2).

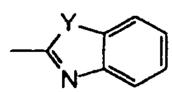
64. The compound according to claim 62, wherein R_1 is (e10-A).

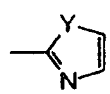
65. A compound represented by the formula:

$-Ar_3$, $-CONH_2$, $-OR_5$, $-OH$, $-OR_9$, or $-CO_2H$;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

Ar_2 is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by $-Q_1$ or phenyl, optionally substituted by Q_1:

(hh)  , and

(ii)  ,

wherein each Y is independently selected from the group consisting of O and S;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, $-N(R_5)-$, and $-N(R_9)-$ said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 is a cyclic group independently selected

$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-NH-R_{10}$,
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-OR_{10}$,
$-C(O)C(O)-R_{10}$,
$-C(O)-CH_2-N(R_{10})(R_{10})$,
$-C(O)-CH_2C(O)-O-R_9$,
$-C(O)-CH_2C(O)-R_9$,
-H, and
$-C(O)-C(O)-OR_{10}$;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{11} is independently selected from the group consisting of:

$-Ar_4$,
$-(CH_2)_{1-3}-Ar_4$,
-H, and
$-C(O)-Ar_4$;

R_{15} is selected from the group consisting of -OH, $-OAr_3$, -N(H)-OH, and $-OC_{1-6}$, wherein C_{1-6} is a straight or branched alkyl group optionally substituted with

cyclopentyl, and cyclohexyl;

R_3 is selected from the group consisting of:

-CN,

-C(O)-H,

-C(O)-CH_2-T_1-R_{11},

-C(O)-CH_2-F,

-C=N-O-R_9, and

-CO-Ar_2;

each R_5 is independently selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

-C(O)-N(R_{10})(R_{10})

-S(O)$_2$-R_9,

-S(O)$_2$-NH-R_{10},

-C(O)-CH_2-O-R_9,

-C(O)C(O)-R_{10},

-R_9,

-H,

-C(O)C(O)-OR_{10}, and

-C(O)C(O)-N(R_9)(R_{10});

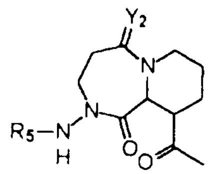
Y_2 is H_2 or O;

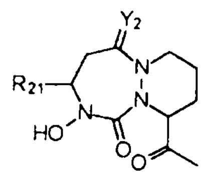
X_7 is -N(R_8)- or -O-;

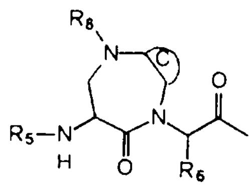
each T_1 is independently selected from the group consisting of -O-, -S-, -S(O)-, and -S(O)$_2$-;

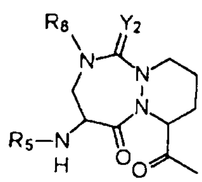
R_6 is selected from the group consisting of -H and -CH_3;

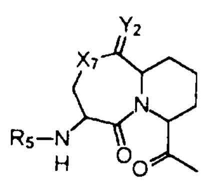
R_8 is selected from the group consisting of:

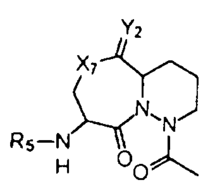
(e11)  ;

(e12)  ;

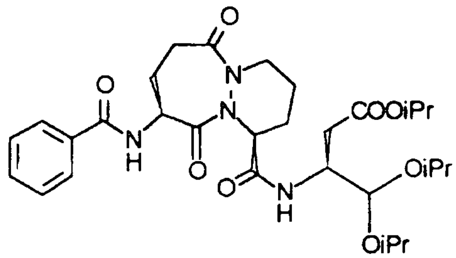
(w2)  ;

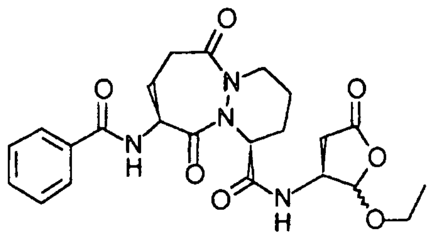
(y1)  ;

(y2)  ; and

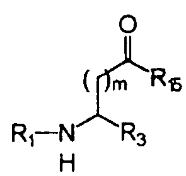
(z)  ;

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo,

2100d  ; and

2100e  .

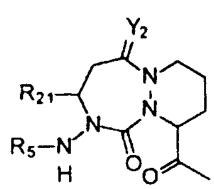
62. A compound represented by the formula:

(IV) 

wherein:

m is 1 or 2;

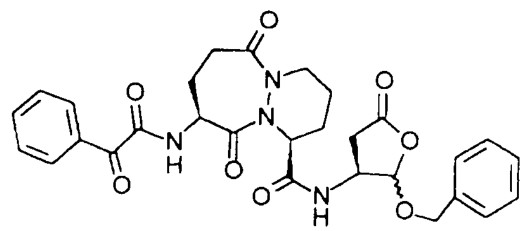
R_1 is selected from the group consisting of the following formulae:

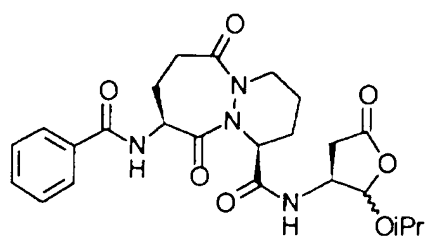
(e10-A)  ;

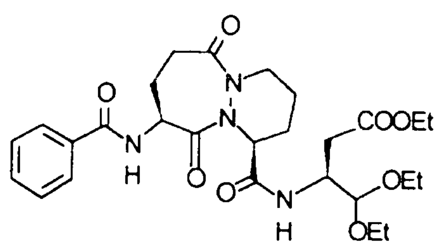
wherein R_1 is (e10) and X_5 is CH.

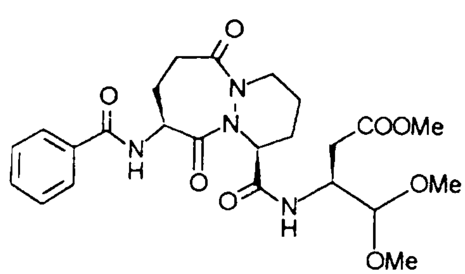
60. The compound according to claim 57, wherein R_1 is (e10) and X_5 is N.

61. The compound according to claim 57, selected from the group consisting of:

2001  ;

2100a  ;

2100b  ;

2100c  ;

each R_{21} is independently selected from the group consisting of -H or a $-C_{1-6}$ straight or branched alkyl group;

each Ar_3 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings and an aromatic heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocyclic group containing at least one heteroatom group selected from -O-, -S-, -SO-, SO_2, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, $-CO_2H$, -Cl, -F, -Br, -I, $-NO_2$, -CN, =O, -OH, -perfluoro C_{1-3} alkyl, R_5, $-OR_5$, $-NHR_5$, $-OR_9$, $-N(R_9)(R_{10})$, $-R_9$, $-C(O)-R_{10}$, and

```
 O
/ \
   CH2,
\ /
 O
```

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

58. The compound according to claim 57, wherein R_1 is (w2).

59. The compound according to claim 57,

R_8 is selected from the group consisting of:

-C(O)-R_{10},

-C(O)O-R_9,

-C(O)-N(H)-R_{10},

-S(O)$_2$-R_9,

-S(O)$_2$-NH-R_{10},

-C(O)-CH_2-OR_{10},

-C(O)C(O)-R_{10};

-C(O)-$CH_2N(R_{10})(R_{10})$,

-C(O)-CH_2C(O)-O-R_9,

-C(O)-CH_2C(O)-R_9,

-H, and

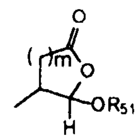
-C(O)-C(O)-OR_{10};

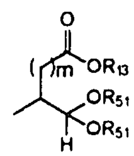
each R_9 is independently selected from the group consisting of -Ar_3 and a -C_{1-6} straight or branched alkyl group optionally substituted with -Ar_3, wherein the -C_{1-6} alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, -Ar_3, a -C_{3-6} cycloalkyl group, and a -C_{1-6} straight or branched alkyl group optionally substituted with -Ar_3, wherein the -C_{1-6} alkyl group is optionally unsaturated;

R_{13} is selected from the group consisting of H, Ar_3, and a -C_{1-6} straight or branched alkyl group optionally substituted with -Ar_3, -$CONH_2$, -OR_5, -OH, -OR_9, or -CO_2H;

each R_{51} is independently selected from the group consisting of R_9, -C(O)-R_9, -C(O)-N(H)-R_9, or each R_{51} taken together forms a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-;

(a)  , or

(b)  ;

m is 1 or 2;

each R_5 is independently selected from the group consisting of:

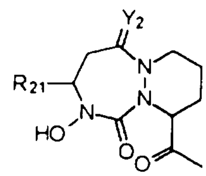
$-C(O)-R_{10}$,
$-C(O)O-R_9$,
$-C(O)-N(R_{10})(R_{10})$
$-S(O)_2-R_9$,
$-S(O)_2-NH-R_{10}$,
$-C(O)-CH_2-O-R_9$,
$-C(O)C(O)-R_{10}$,
$-R_9$,
$-H$,
$-C(O)C(O)-OR_{10}$, and
$-C(O)C(O)-N(R_9)(R_{10})$;

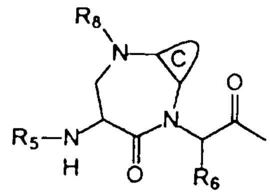
X_5 is CH or N;

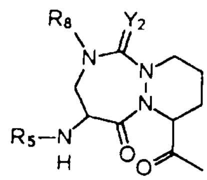
Y_2 is H_2 or O;

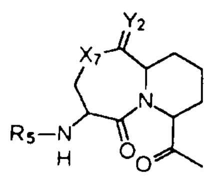
X_7 is $-N(R_8)-$ or $-O-$;

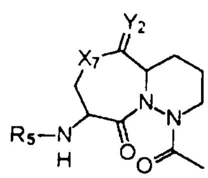
R_6 is selected from the group consisting of -H and $-CH_3$;

(e12)  ;

(w2)  ;

(y1)  ;

(y2)  ;

(z)  ; and

ring C is chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_2 is:

atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke in a patient comprising the step of administering to said patient a pharmaceutical composition according to any one of claims 42 to 54.

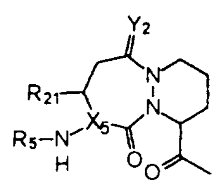
56. The method according to claim 55, wherein the disease is selected from the group consisting of osteoarthritis, acute pancreatitis, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, psoriasis, and Alzeheimer's disease.

57. A compound represented by the formula:

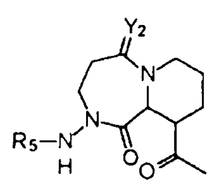
$$\text{(III)} \qquad R_1\text{-}\underset{\displaystyle H}{\underset{|}{N}}\text{-}R_2$$

wherein:

R_1 is selected from the group consisting of the following formulae:

(e10) 

;

(e11) 

;

to claim 43, wherein the apoptosis-mediated disease is a degenerative disease, selected from the group consisting of Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

54. A pharmaceutical composition for inhibiting an ICE-mediated function comprising an ICE inhibitor according to any one of claims 1-41 and 57-135 and a pharmaceutically acceptable carrier.

55. A method for treating or preventing a disease selected from the group consisting of an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a necrotic disease, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular

47. The pharmaceutical composition according to claim 46, wherein the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, or Crohn's disease, or psoriasis.

48. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a destructive bone disorder selected from the group consisting of osteoporosis or multiple myeloma-related bone disorder.

49. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a proliferative disorder selected from the group consisting of acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

50. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an infectious disease, selected from the group consisting of sepsis, septic shock, and Shigellosis.

51. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is a degenerative or necrotic disease, selected from the group consisting of Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia.

52. The pharmaceutical composition according to claim 51, wherein the degenerative disease is Alzheimer's disease.

53. The pharmaceutical composition according

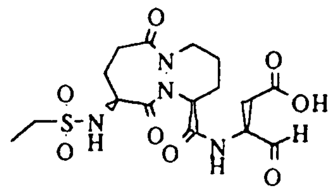
an ICE inhibitor according to any one of claims 1-41 and 57-135 in an amount effective for treating or preventing an IL-1-mediated disease and a pharmaceutically acceptable carrier.

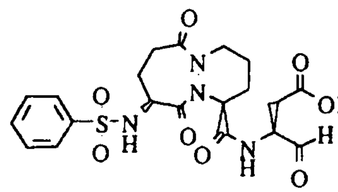
43. A pharmaceutical composition comprising an ICE inhibitor according to any one of claims 1-41 and 57-135 in an amount effective for treating or preventing an apoptosis-mediated disease and a pharmaceutically acceptable carrier.

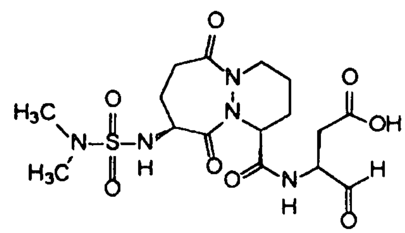
44. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an inflammatory disease selected from the group consisting of osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, and adult respiratory distress syndrome.

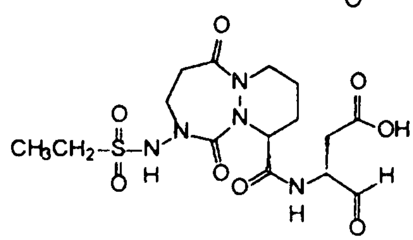
45. The pharmaceutical composition according to claim 44, wherein the inflammatory disease is osteoarthritis or acute pancreatitis.

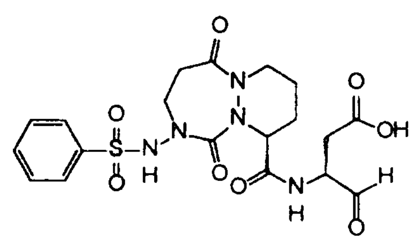
46. The pharmaceutical composition according to claim 42, wherein the IL-1-mediated disease is an autoimmune disease selected from the group consisting of glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, and graft vs host disease.

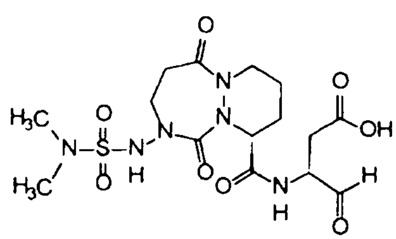
421  ;

427  ;

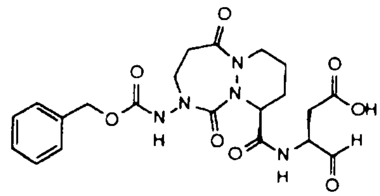
428  ;

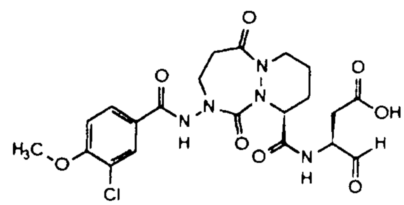
1021  ;

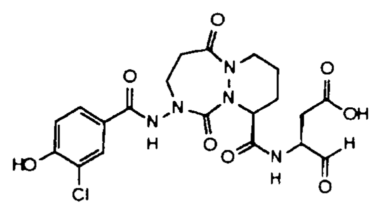
1027  ; and

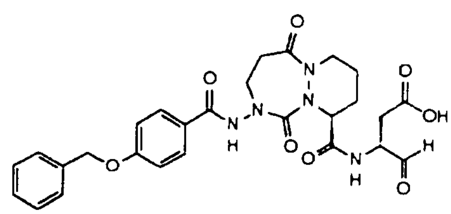
1028  .

42. A pharmaceutical composition comprising

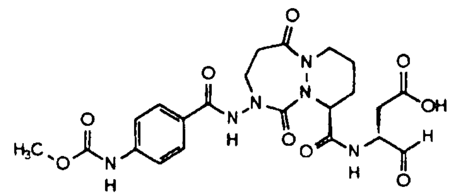
1096  ;

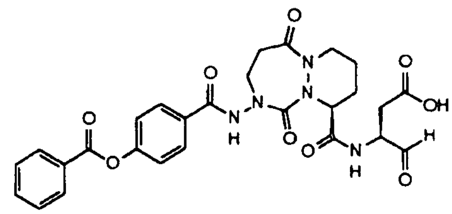
1097  ;

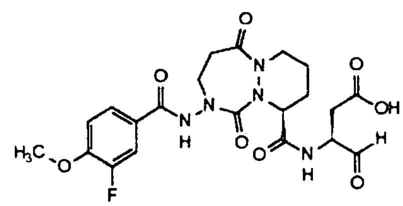
1098  ; and

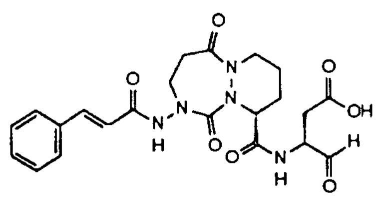
1099  .

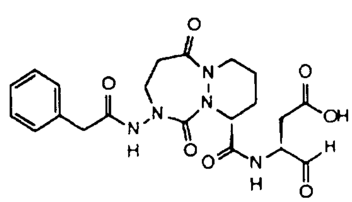
41. The compound according to claim 33 selected from the group consisting of:

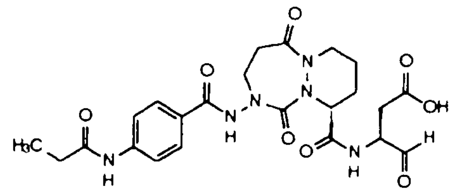
1090  ;

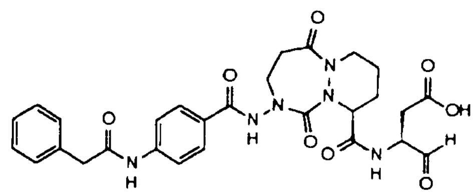
1091  ;

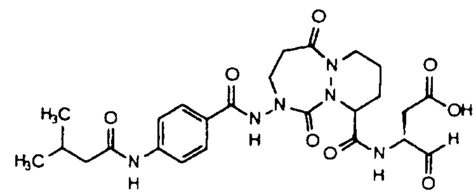
1093  ;

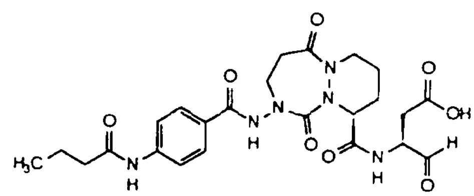
1094  ;

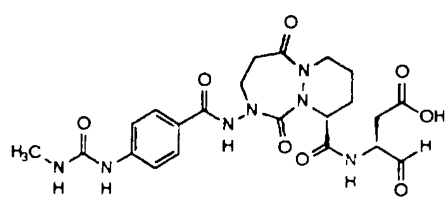
1095  ;

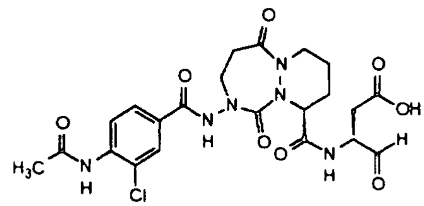
1085  ;

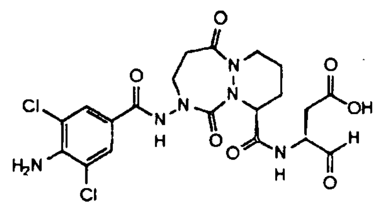
1086  ;

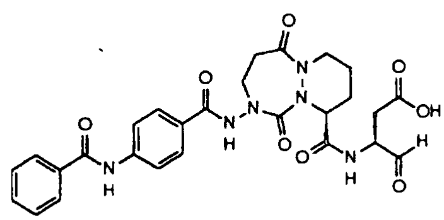
1087  ;

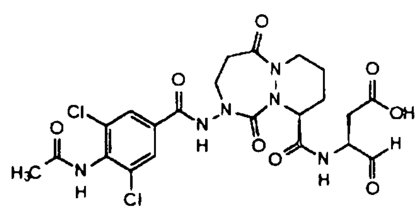
1088  ;

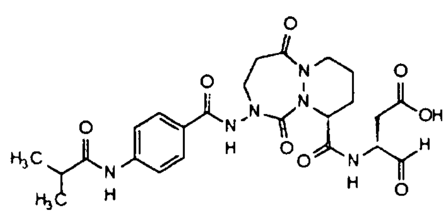
1089  ;

1081s  ;

1082  ;

1083  ;

1082s  ;

1084  ;

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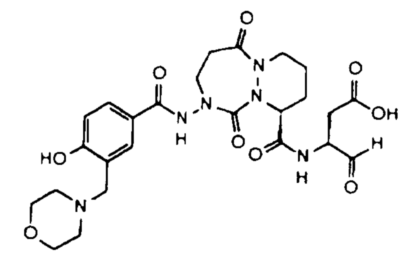

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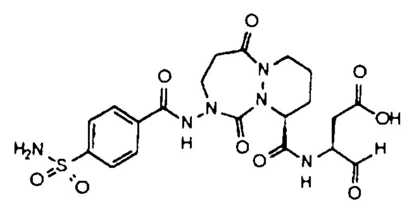

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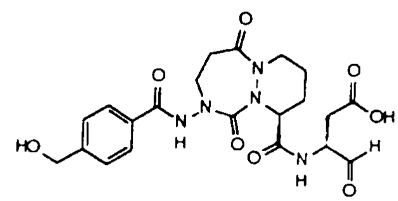

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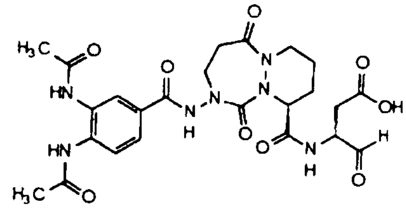

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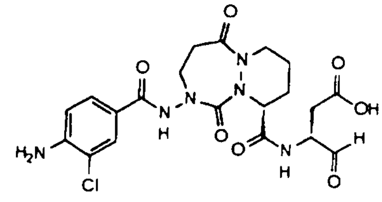

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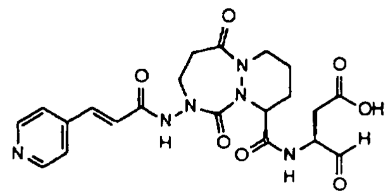
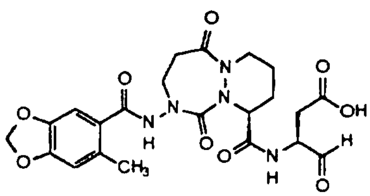
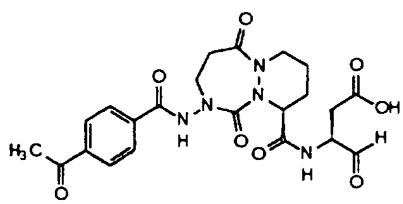
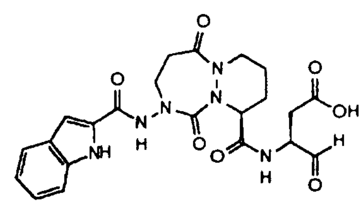
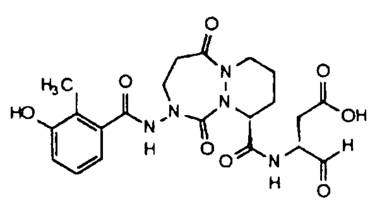
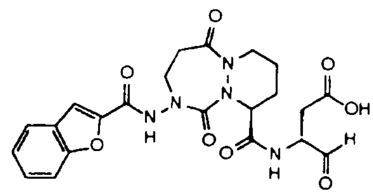
1072  ;

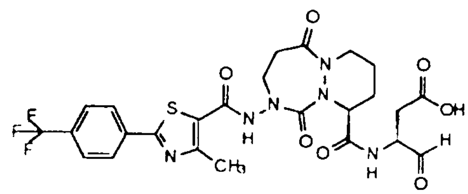
1073  ;

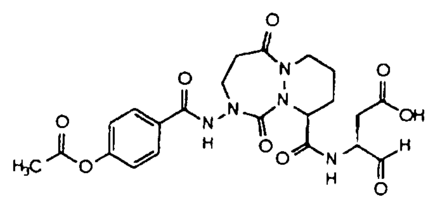
1074  ;

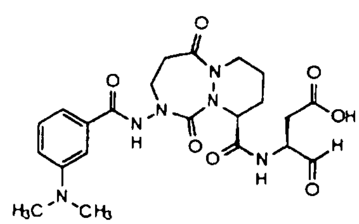
1075  ;

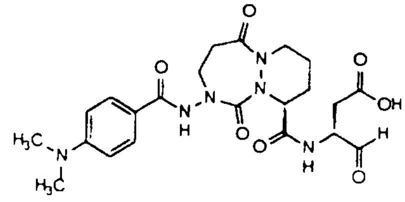
1076  ;

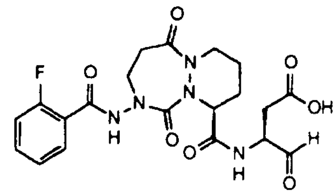
1067  ;

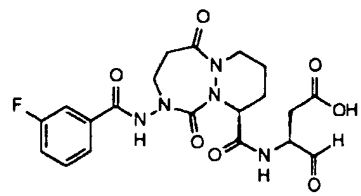
1068  ;

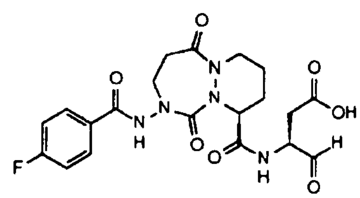
1069  ;

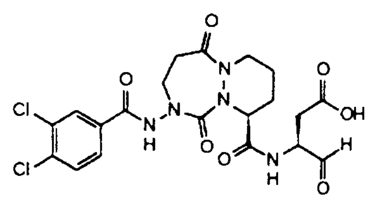
1070  ;

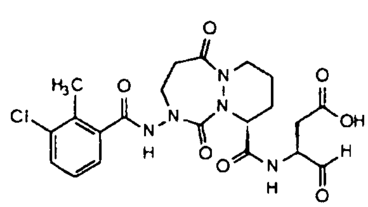
1071  ;

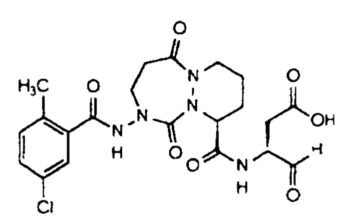
1061  ;

1062  ;

1063  ;

1064  ;

1065  ;

1066  ;

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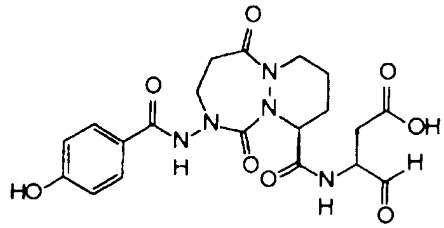

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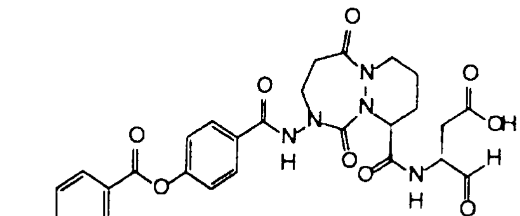

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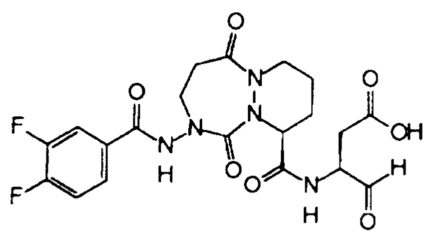

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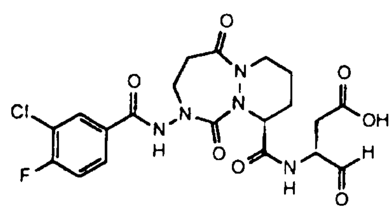

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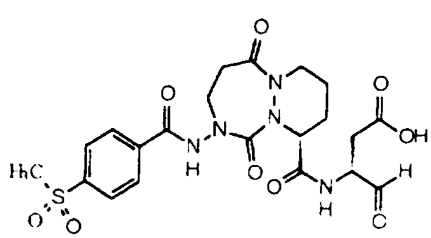

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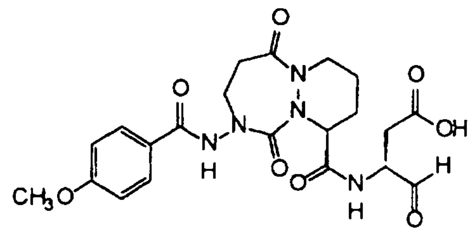
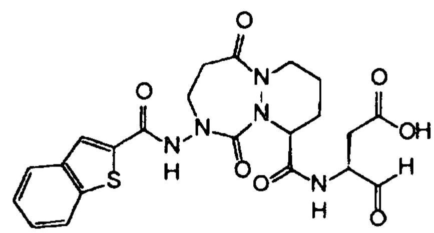
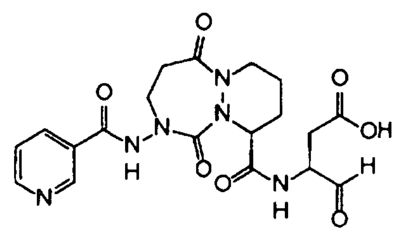
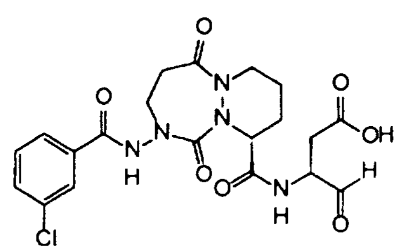
1052  ;

1053  ;

1054  ;

1055  ;

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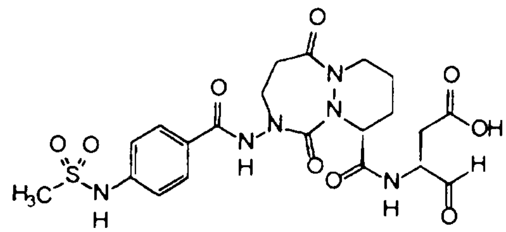

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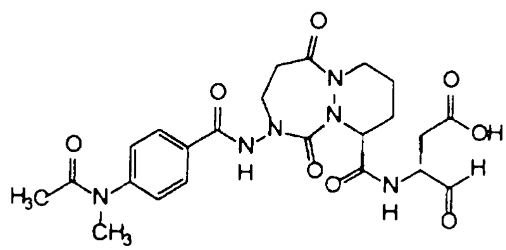

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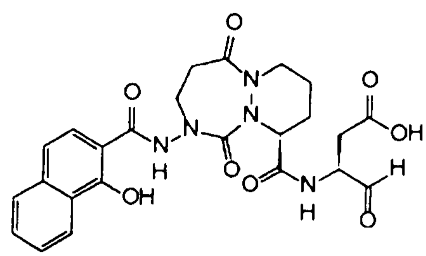

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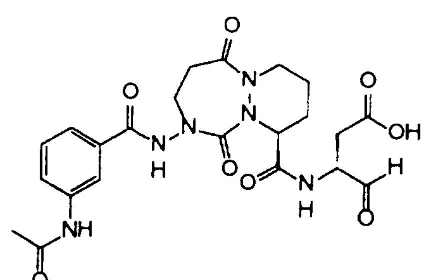

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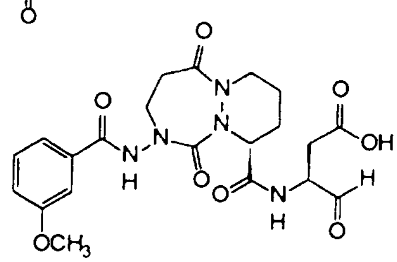

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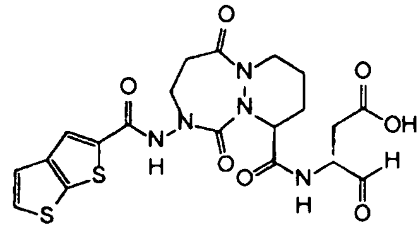
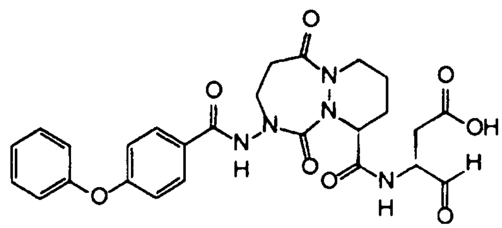
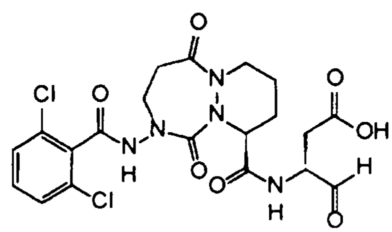
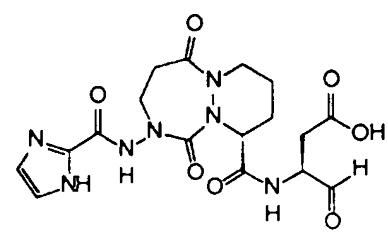
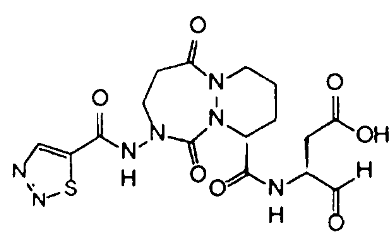
1042  ;

1043  ;

1044  ;

1045  ;

1046  ;

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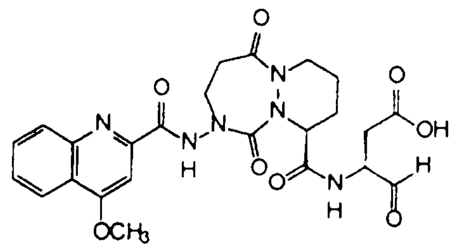

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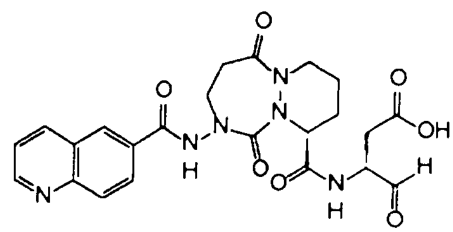

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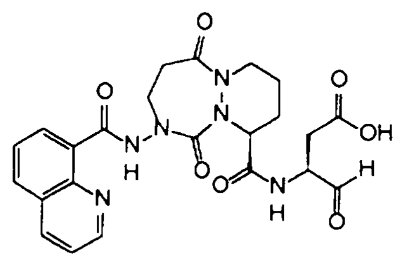

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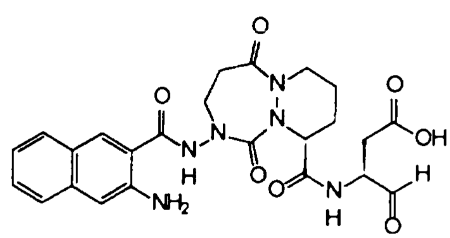

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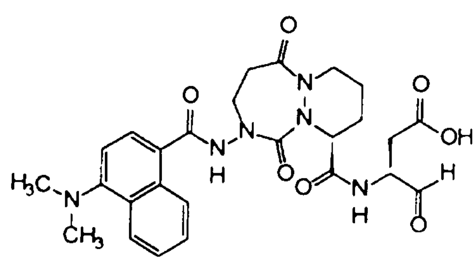

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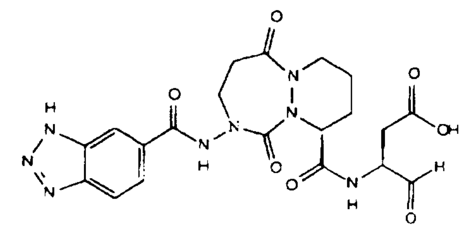
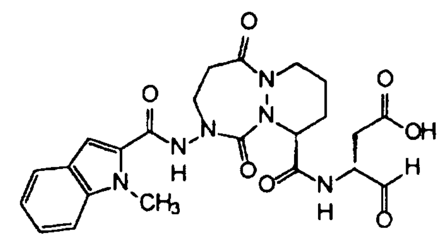
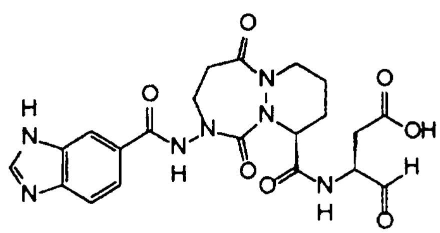
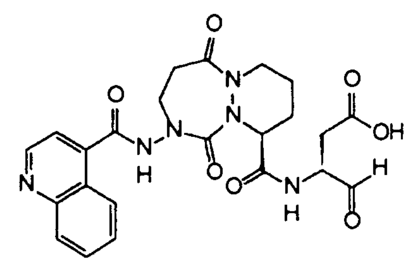
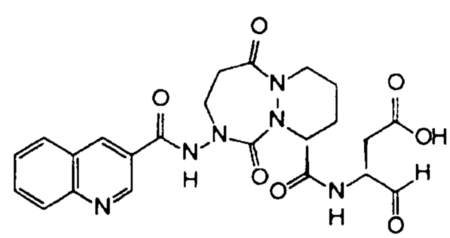
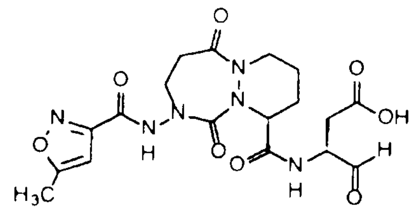
1032  ;

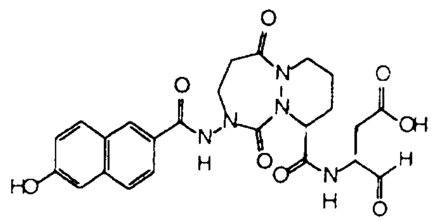
1033  ;

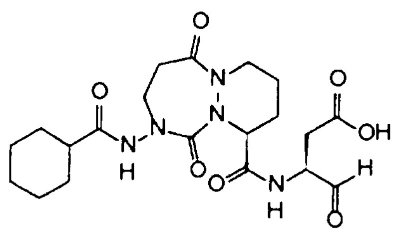
1034  ;

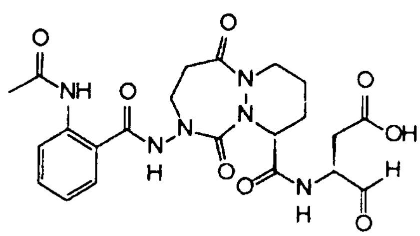
1035  ;

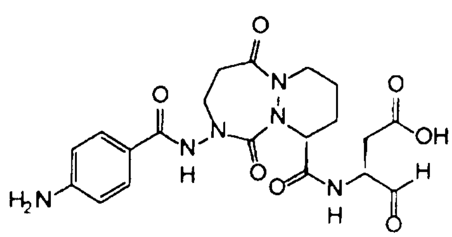
1036  ;

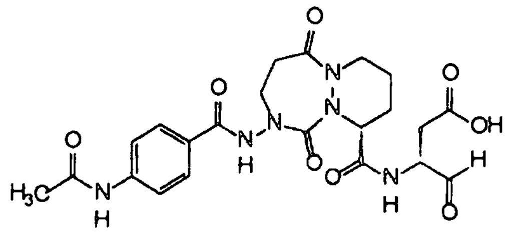
1024  ;

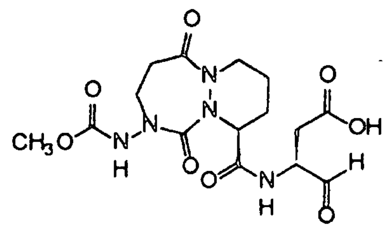
1025  ;

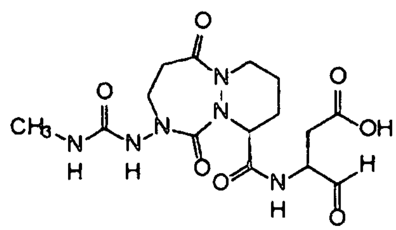
1026  ;

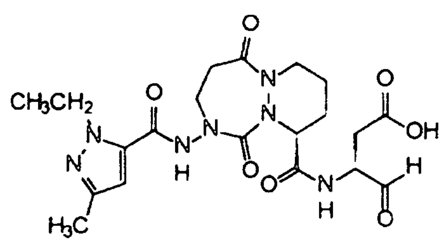
1030  ;

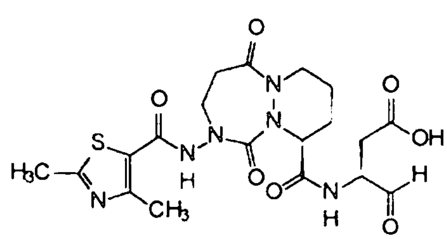
1031  ;

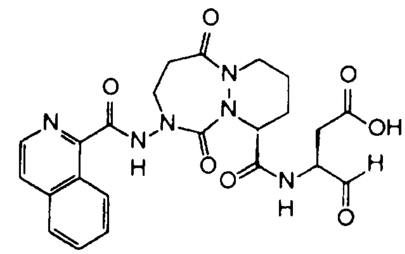
1018  ;

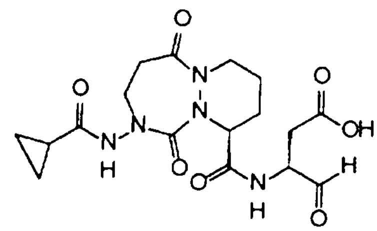
1019  ;

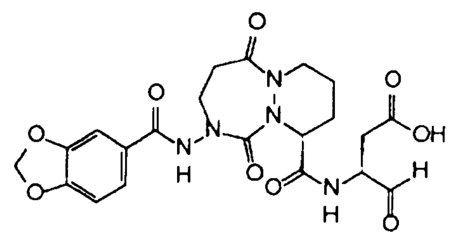
1020  ;

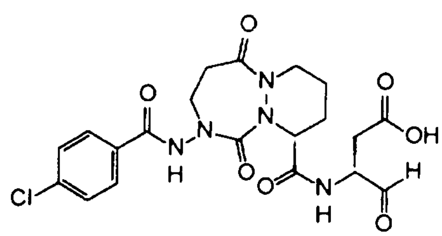
1022  ;

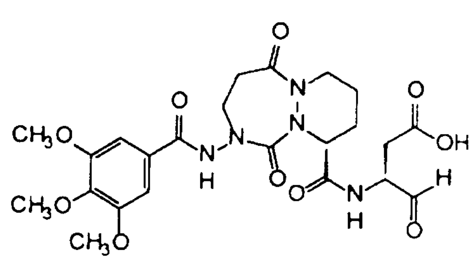
1023  ;

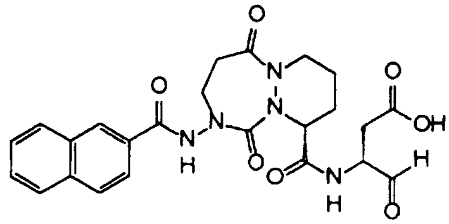
1012  ;

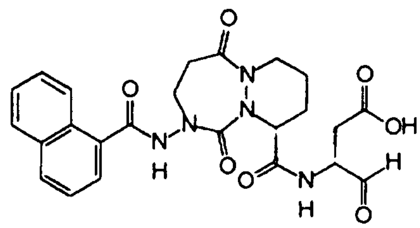
1013  ;

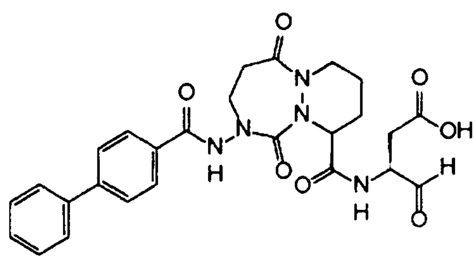
1015  ;

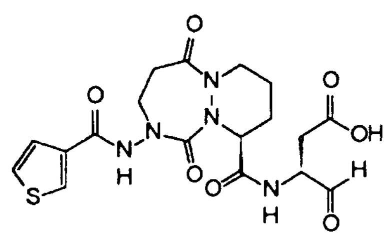
1016  ;

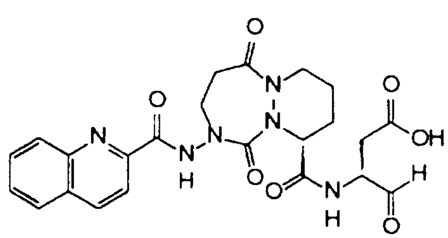
1017  ;

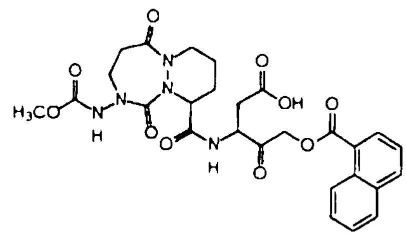
1007  ;

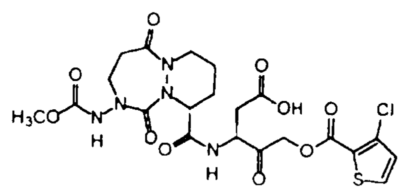
1008  ;

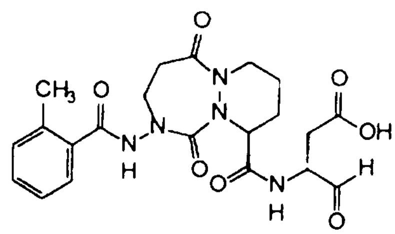
1009  ;

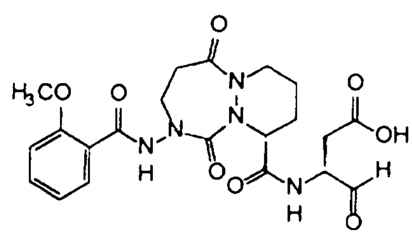
1010  ;

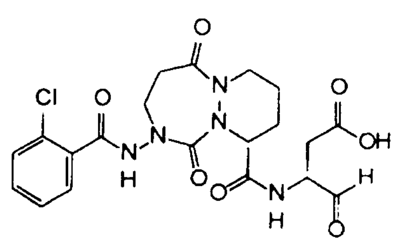
1011  ;

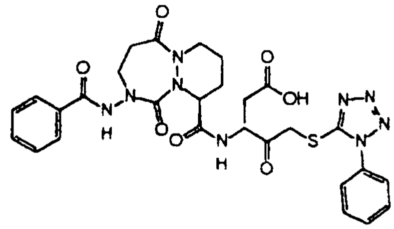
886  ;

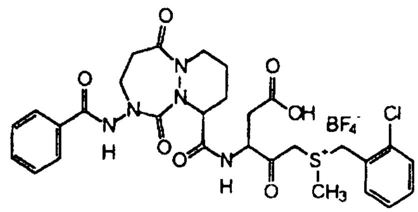
887  ;

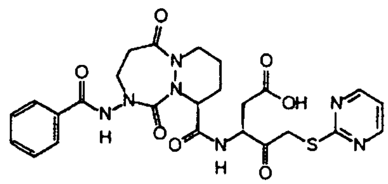
1004  ;

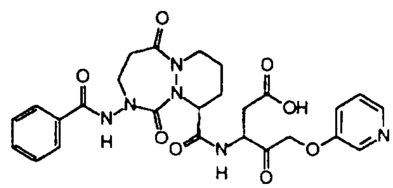
1005  ;

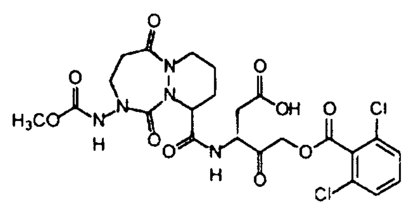
1006  ;

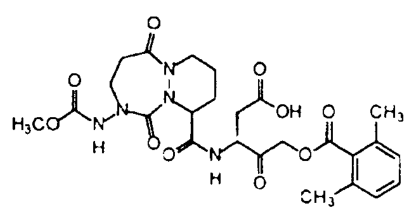
880  ;

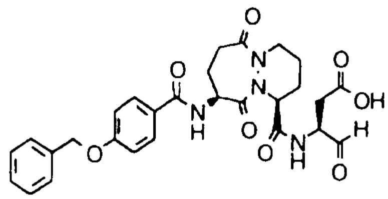
881  ;

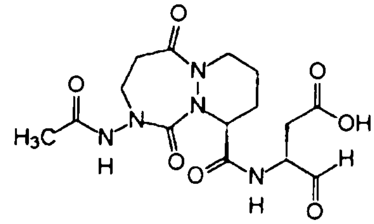
882  ;

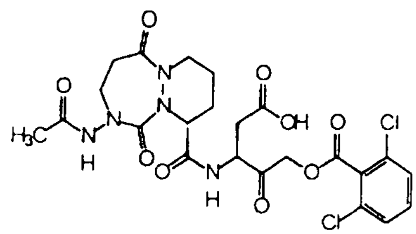
883  ;

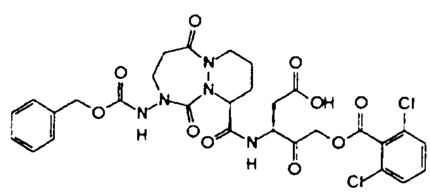
884  ;

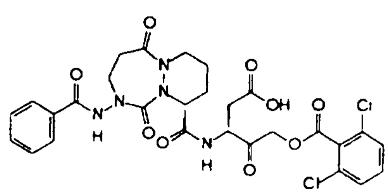
885  ;

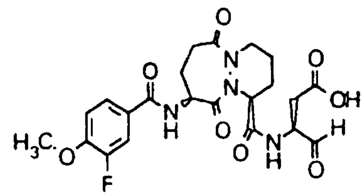
499  ;

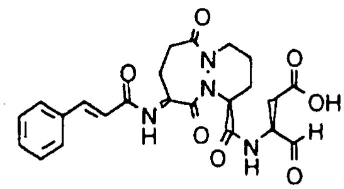
814c  ;

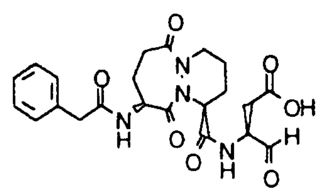
817c  ;

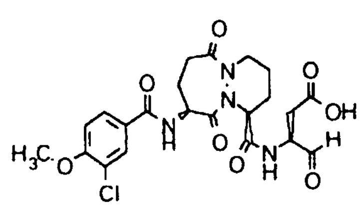
817d  ;

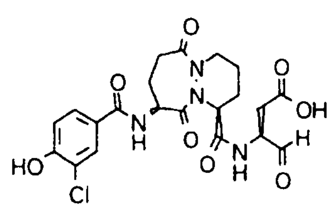
817e  ;

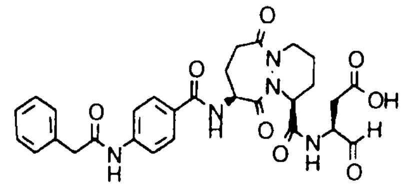
493  ;

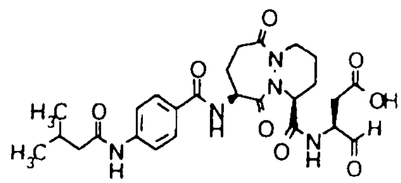
494  ;

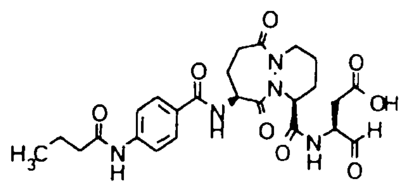
495  ;

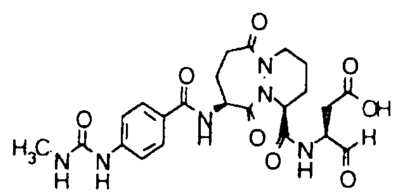
497  ;

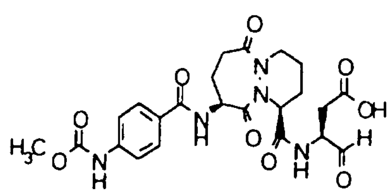
498  ;

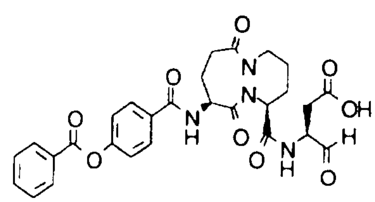
486  ;

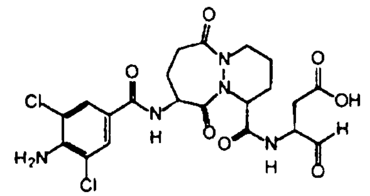
487  ;

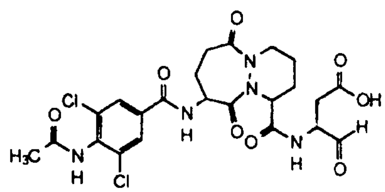
488  ;

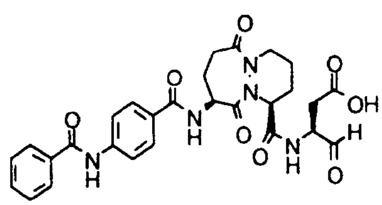
489  ;

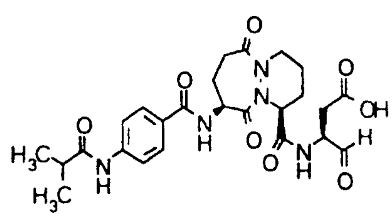
490  ;

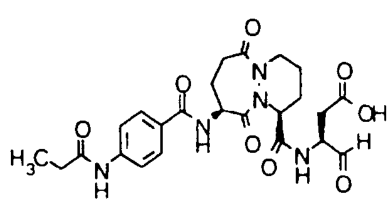
491  ;

482  ;

482s  ;

483  ;

484  ;

485  ;

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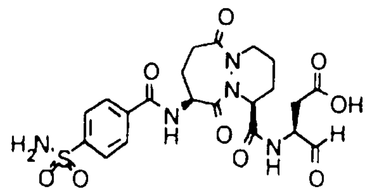

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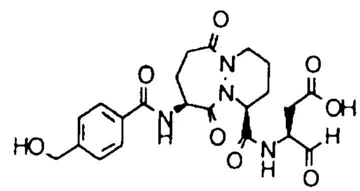

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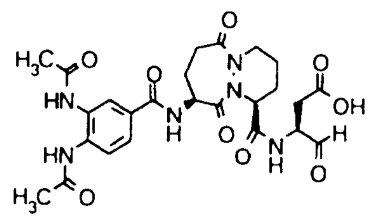

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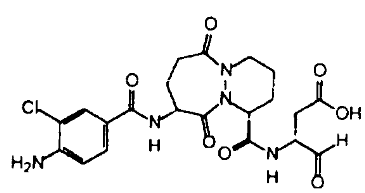

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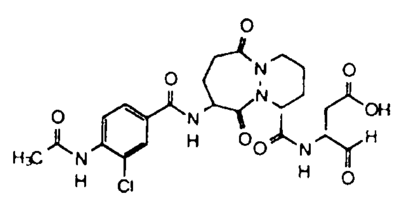

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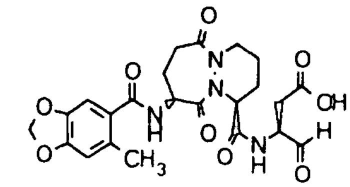

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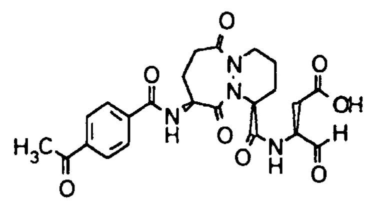

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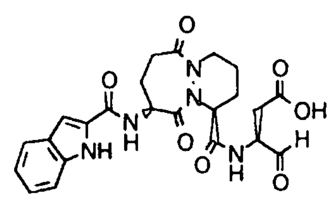

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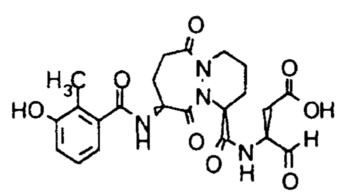

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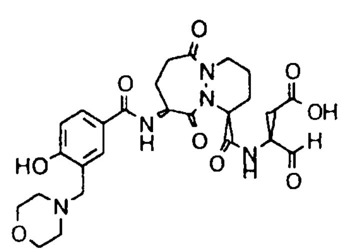

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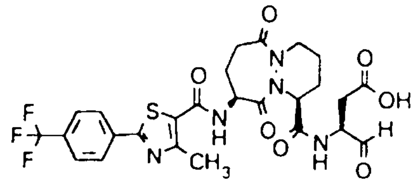
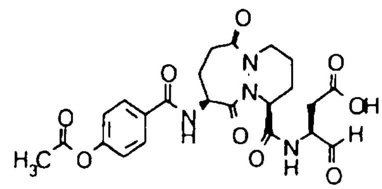
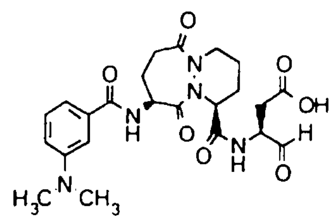
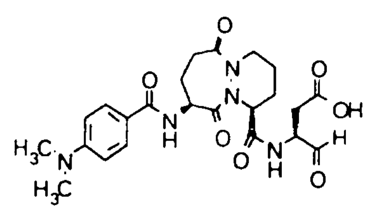
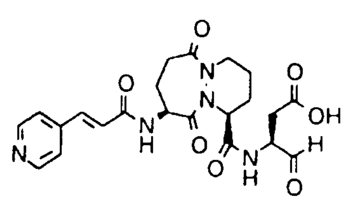
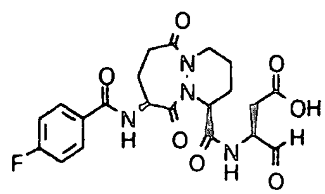
468  ;

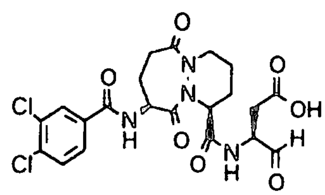
469  ;

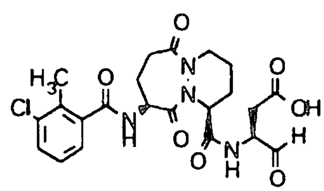
470  ;

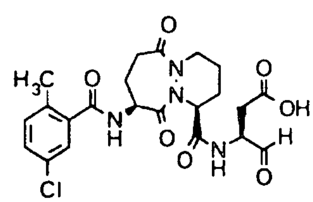
471  ;

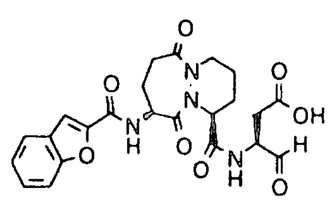
472  ;

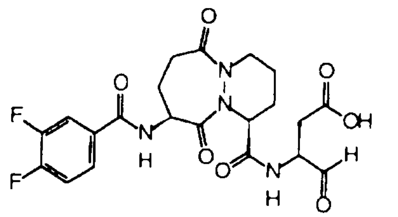
463  ;

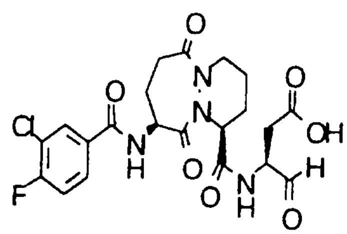
464  ;

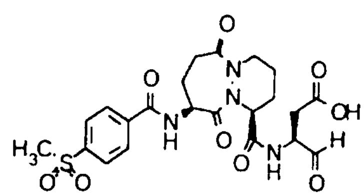
465  ;

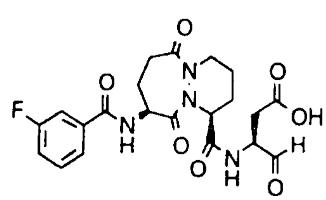
466  ;

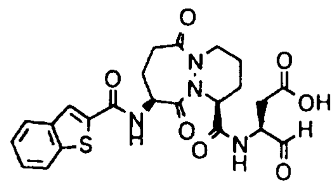
467  ;

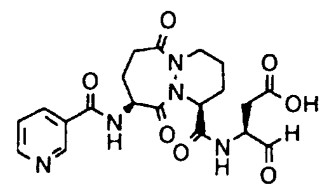
458  ;

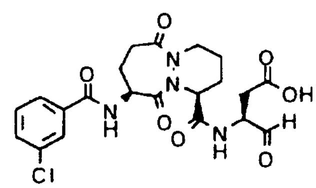
459  ;

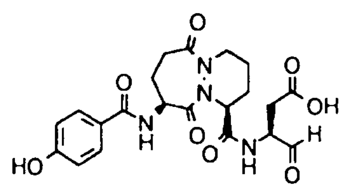
460  ;

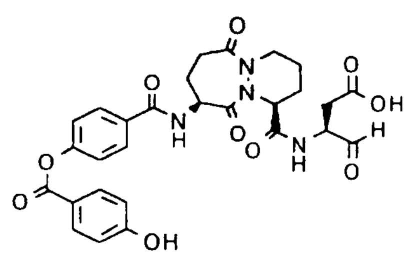
462  ;

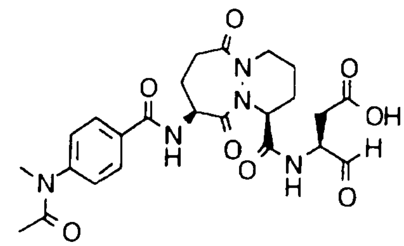
453  ;

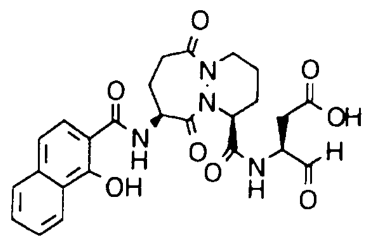
454  ;

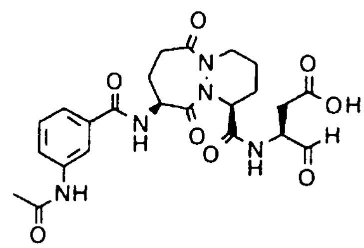
455  ;

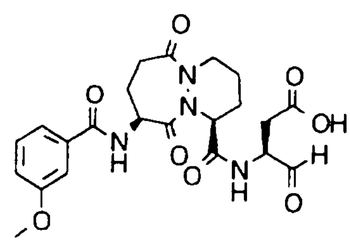
456  ;

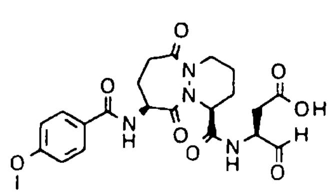
457  ;

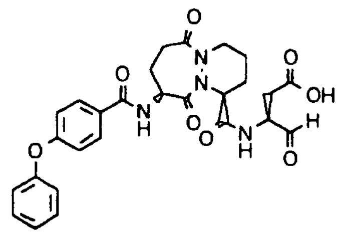
448  ;

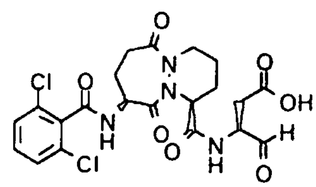
449  ;

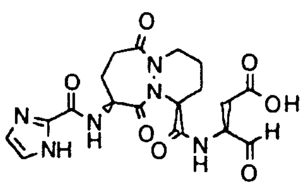
450  ;

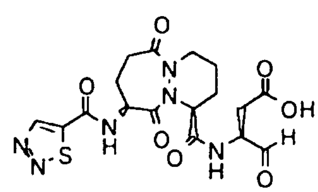
451  ;

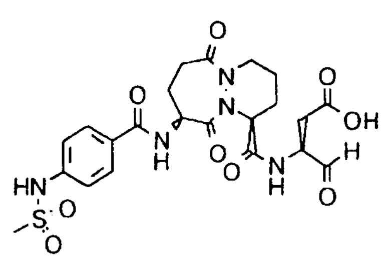
452  ;

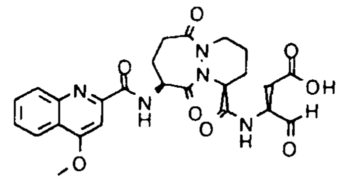
443  ;

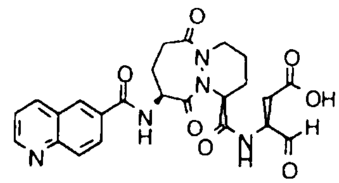
444  ;

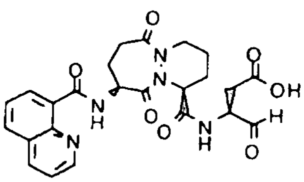
445  ;

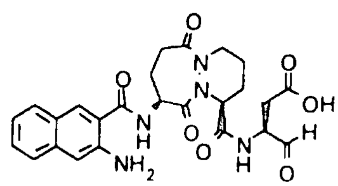
446  ;

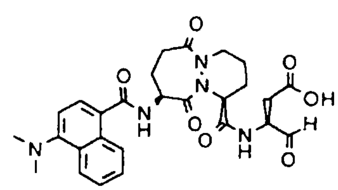
447  ;

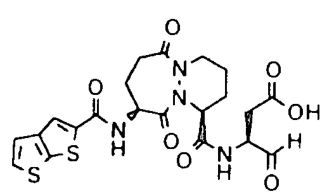
437  ;

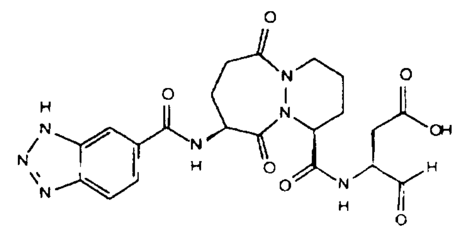
438  ;

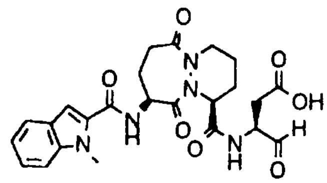
439  ;

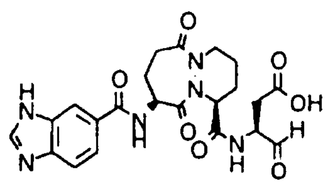
440  ;

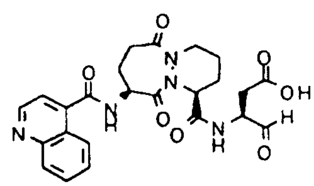
441  ;

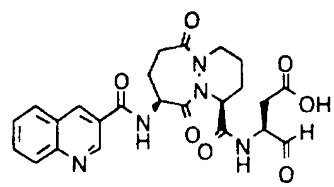
442  ;

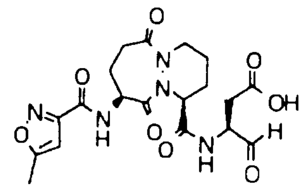
432  ;

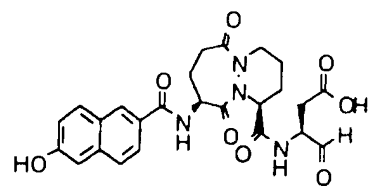
433  ;

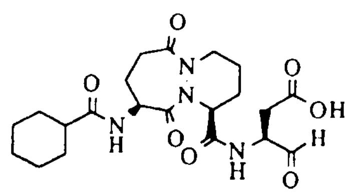
434  ;

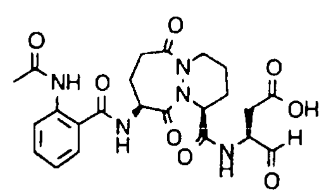
435  ;

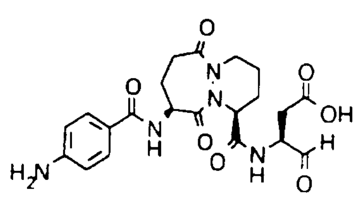
436  ;

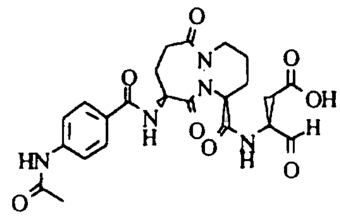
424  ;

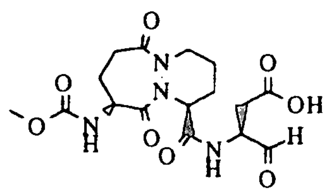
425  ;

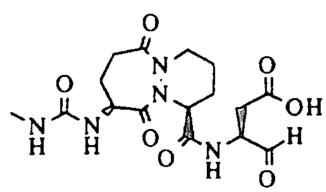
426  ;

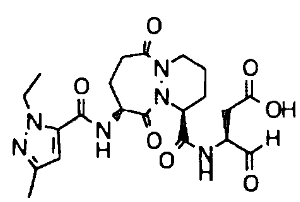
430  ;

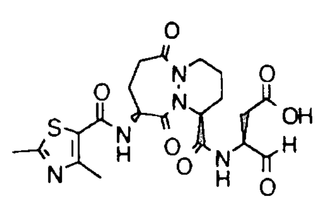
431  ;

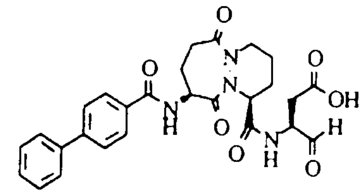
418  ;

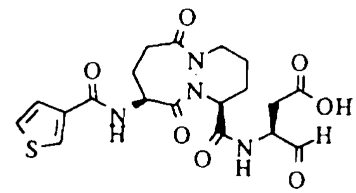
419  ;

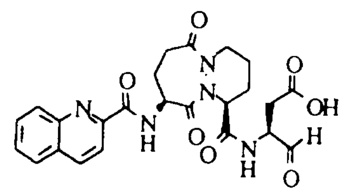
420  ;

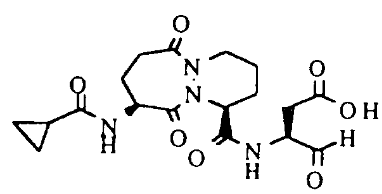
422  ;

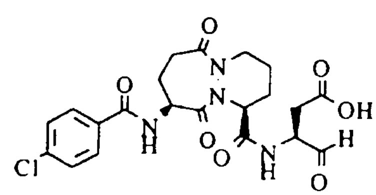
423  ;

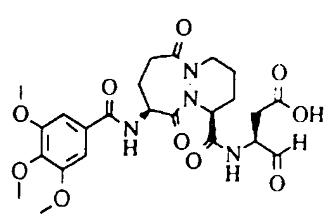
409  ;

410  ;

411  ;

413  ;

416  ;

417  ;

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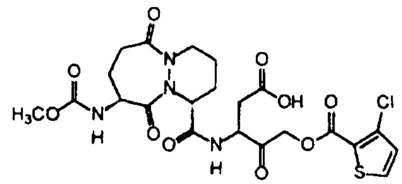

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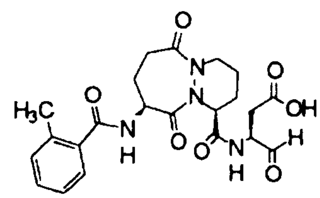

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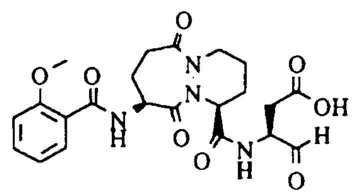

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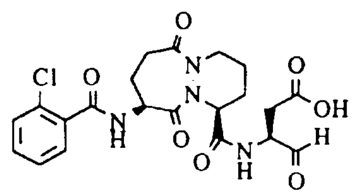

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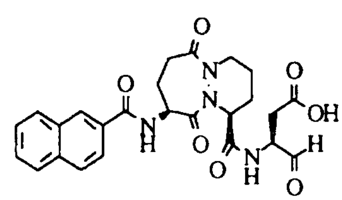

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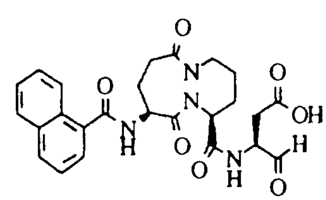

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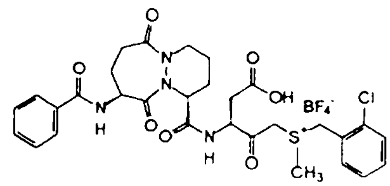
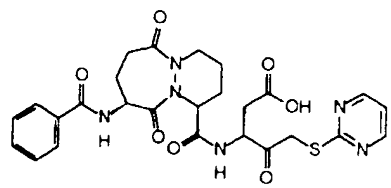
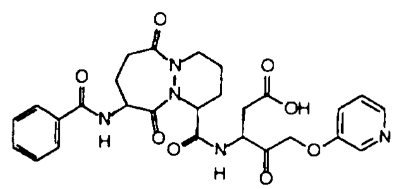
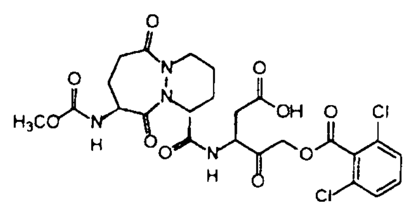
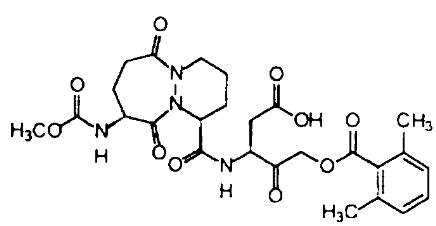
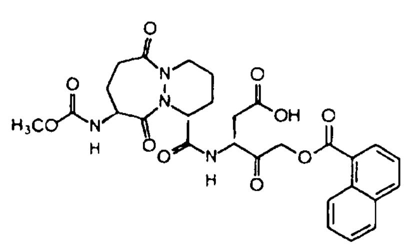
281  ;

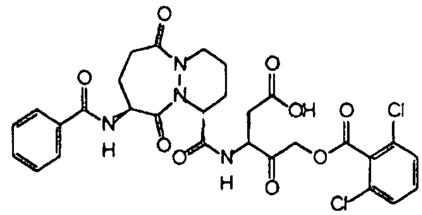
282  ;

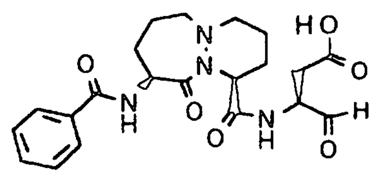
283  ;

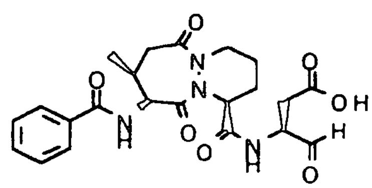
284  ;

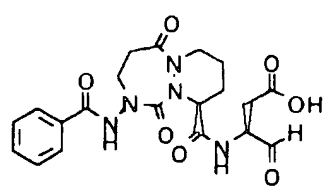
285  ;

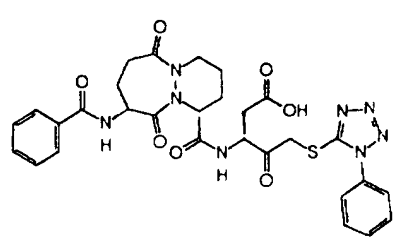
286  ;

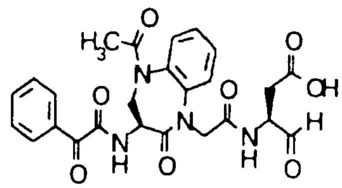
217e  ;

246  ;

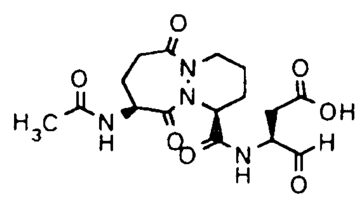
257  ;

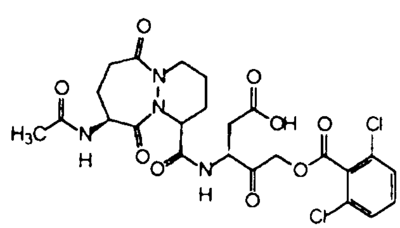
265  ;

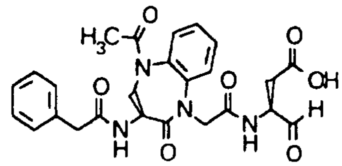
280  ;

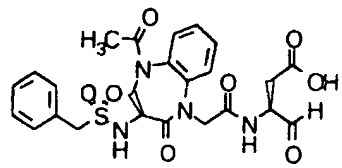
635  .

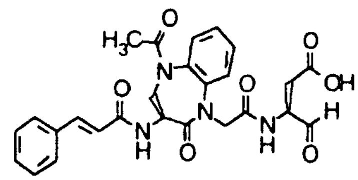
40. The compound according to claims 8 or 68, selected from the group consisting of:

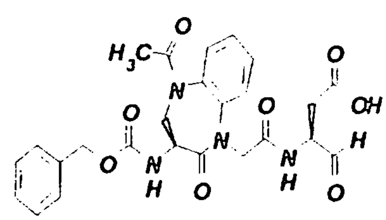
214c  ;

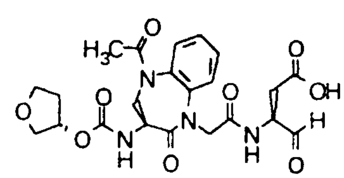
217c  ;

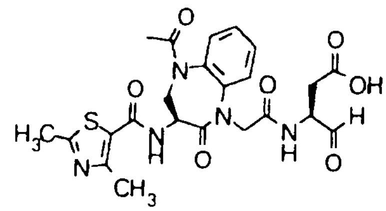
630  ;

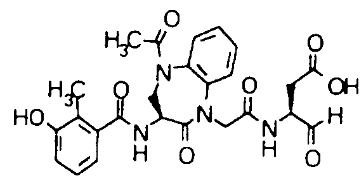
631  ;

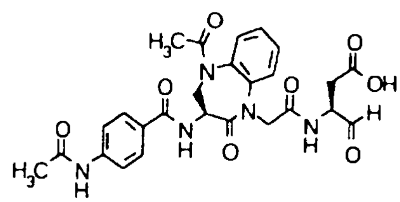
632  ;

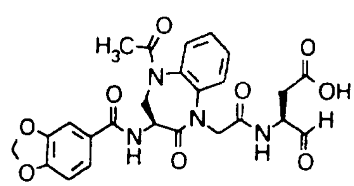
633  ;

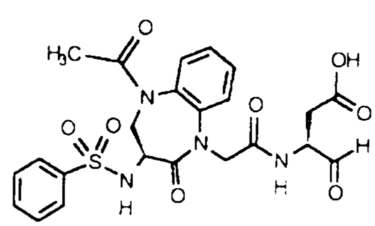
634  ; and

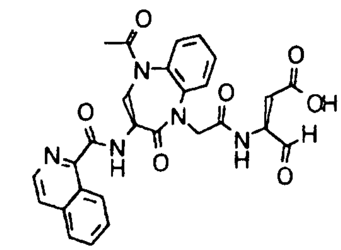
625  ;

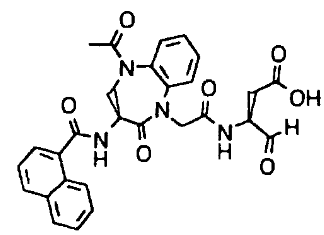
626  ;

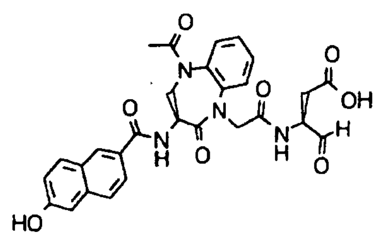
627  ;

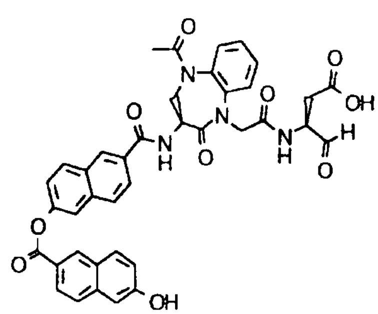
628  ;

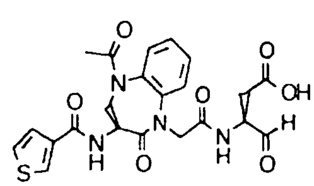
629  ;

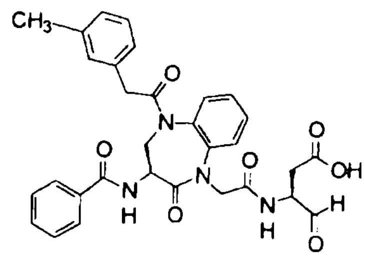
620  ;

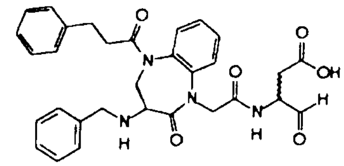
621  ;

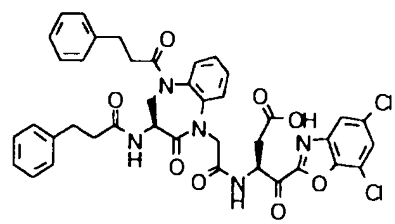
622  ;

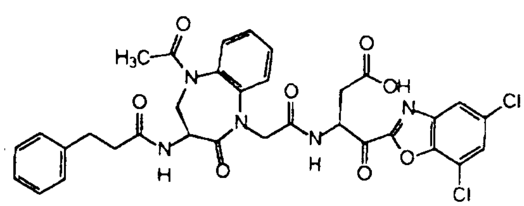
623  ;

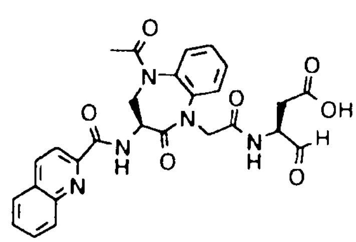
624  ;

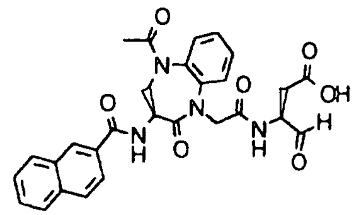
605t  ;

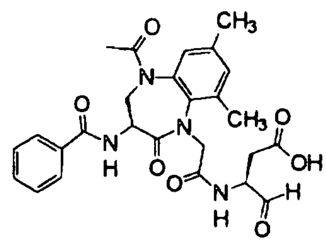
605v  ;

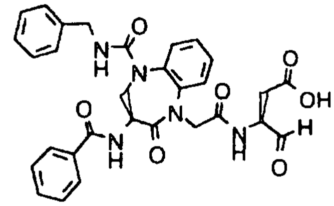
609a  ;

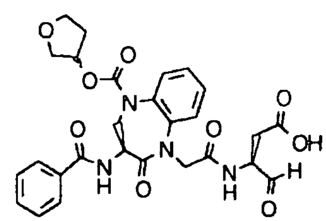
609b  ;

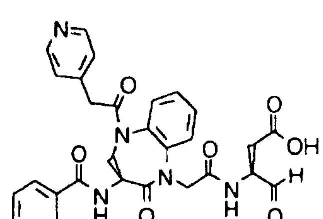
619  ;

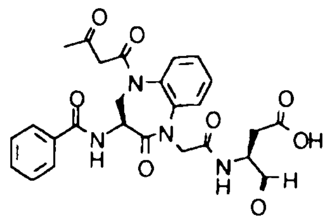
605n  ;

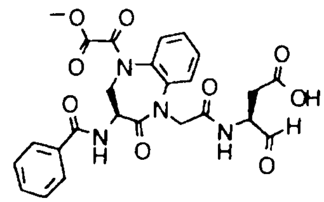
605o  ;

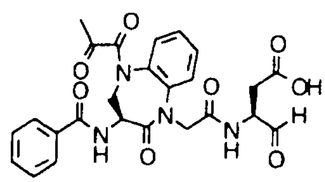
605p  ;

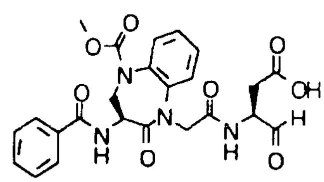
605q  ;

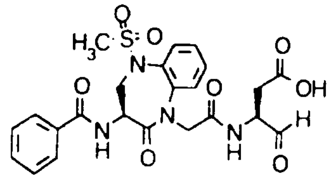
605s  ;

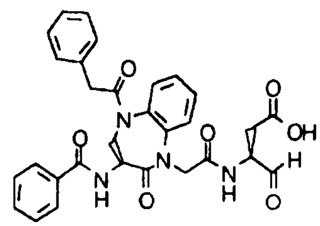
605g  ;

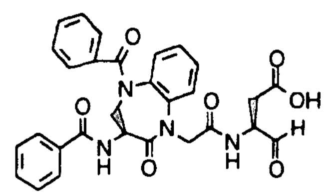
605h  ;

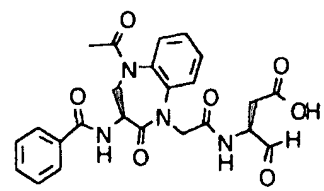
605i  ;

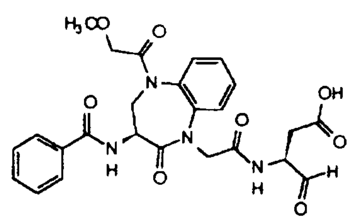
605j  ;

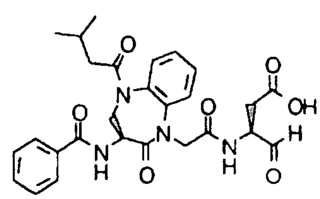
605m  ;

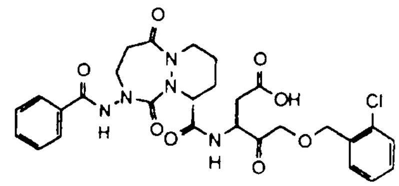
605b  ;

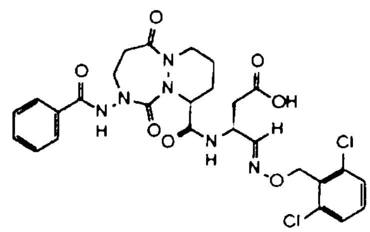
605c  ;

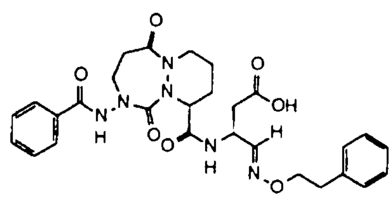
605d  ;

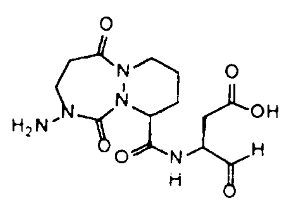
605e  ;

605f  ;

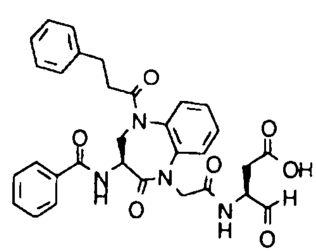
827e  ;

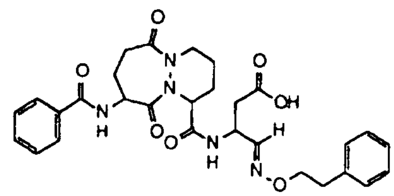
907a  ;

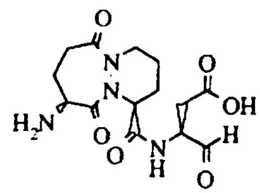
907b  ; and

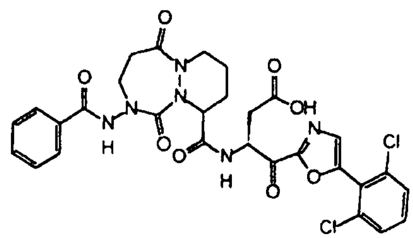
1029  .

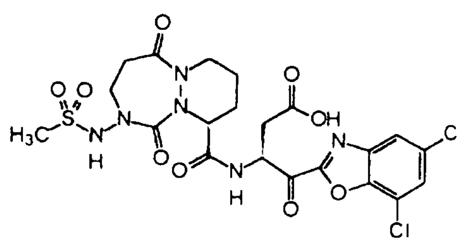
39. The compound according to claim 15 selected from the group consisting of:

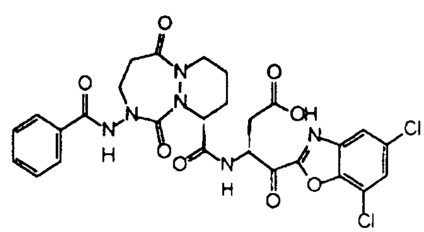
605a  ;

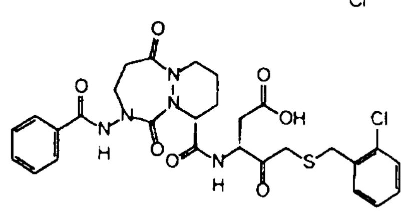
307b  ;

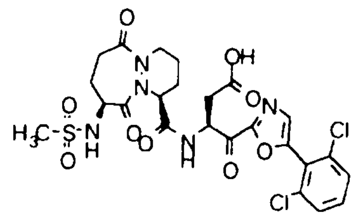
429  ;

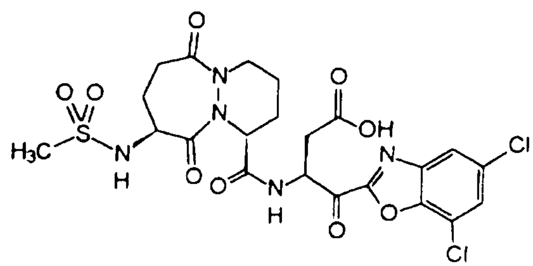
820b  ;

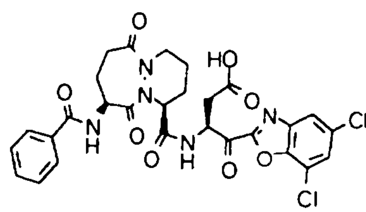
823b  ;

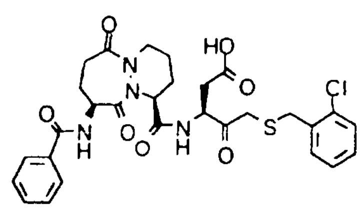
823e  ;

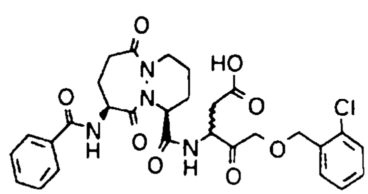
826e  ;

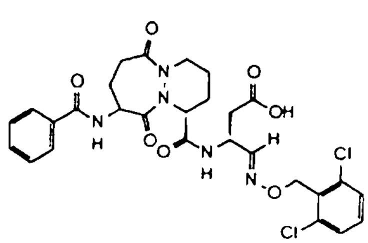
220b  ;

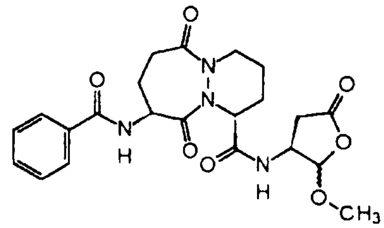
223b  ;

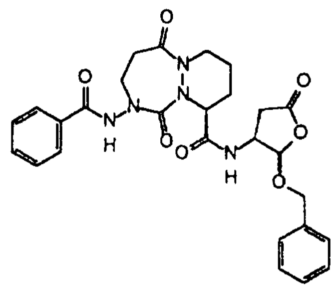
223e  ;

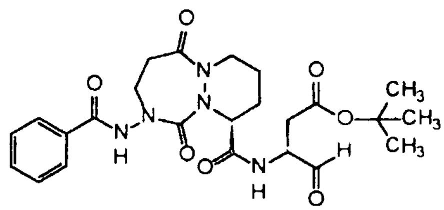
226e  ;

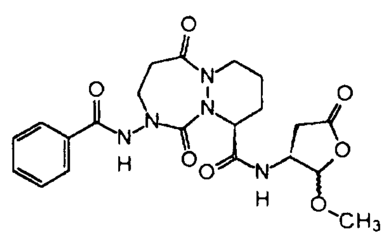
227e  ;

307a  ;

304a  ;

813e  ;

902  ; and

904a  .

38. The compound according to claims 8 or 68, selected from the group consisting of:

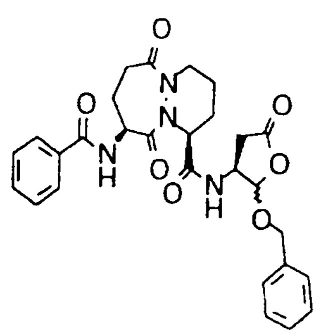
each Q_1 is independently selected from the group consisting of $-NH_2$, $-Cl$, $-F$, $-Br$, $-OH$, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

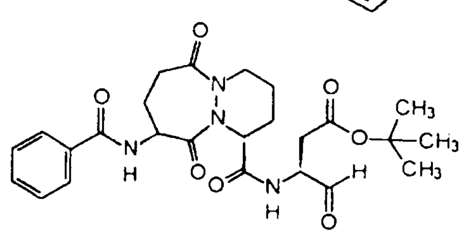
```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$ groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

37. The compound according to claim 7 selected from the group consisting of:

213e  ;

302  ;

each R_9 is independently selected from the group consisting of $-Ar_3$ and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

each R_{10} is independently selected from the group consisting of -H, $-Ar_3$, a $-C_{3-6}$ cycloalkyl group, and a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$, wherein the $-C_{1-6}$ alkyl group is optionally unsaturated;

R_{13} is H or a C_{1-4} straight or branched alkyl group optionally substituted with $-Ar_3$, -OH, $-OR_9$, $-CO_2H$, wherein the R_9 is a C_{1-4} branched or straight chain alkyl group; wherein Ar_3 is morpholinyl or phenyl, wherein the phenyl is optionally substituted with Q_1;

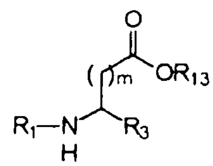
R_{21} is -H or $-CH_3$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

groups, said additional $-Ar_3$ groups are not substituted with another $-Ar_3$.

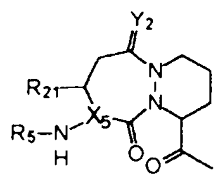
36. A compound represented by the formula:

(II) 

wherein:

m is 1;

R_1 is:

(e10)  ;

R_3 is $-CO-CH_2-T_1-R_{11}$ and R_{11} is $-Ar_4$;

R_5 is selected from the group consisting of:

$-S(O)_2-R_9$,

$-S(O)_2-NH-R_{10}$,

$-C(O)-C(O)-R_{10}$,

$-R_9$, and

$-C(O)-C(O)-OR_{10}$;

X_5 is CH;

Y_2 is O;

T_1 is O or S;

wherein the phenyl is optionally substituted with Q_1;

R_{21} is -H or $-CH_3$;

each Ar_3 cyclic group is independently selected from the set consisting of phenyl, naphthyl, thienyl, quinolinyl, isoquinolinyl, pyrazolyl, thiazolyl, isoxazolyl, benzotriazolyl, benzimidazolyl, thienothienyl, imidazolyl, thiadiazolyl, benzo[b]thiophenyl, pyridyl, benzofuranyl, and indolyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Ar_4 cyclic group is independently selected from the set consisting of phenyl, tetrazolyl, pyridinyl, oxazolyl, naphthyl, pyrimidinyl, and thienyl, and said cyclic group optionally being singly or multiply substituted by $-Q_1$;

each Q_1 is independently selected from the group consisting of $-NH_2$, -Cl, -F, -Br, -OH, $-R_9$, $-NH-R_5$ wherein R_5 is $-C(O)-R_{10}$ or $-S(O)_2-R_9$, $-OR_5$ wherein R_5 is $-C(O)-R_{10}$, $-OR_9$, $-NHR_9$, and

```
  O
 / \
    CH2,
 \ /
  O
```

wherein each R_9 and R_{10} are independently a $-C_{1-6}$ straight or branched alkyl group optionally substituted with $-Ar_3$ wherein Ar_3 is phenyl;

provided that when $-Ar_3$ is substituted with a Q_1 group which comprises one or more additional $-Ar_3$